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Alkaline Degradation of 1,5-Anhydrocellobiitol

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ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL

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SUMMARY

Cellulose is generally considered to degrade by two primary pathways in alkaline media. The first of these pathways involves the progressive removal of glucosyl groups from the reducing end of the polymer chain by β-alkoxy elimination (peeling). The second pathway involves the random cleavage of the glycosidic linkage. Random cleavage of the β-1,4-glycosidic linkage in a cellulose model compound, 1,5-anhydrocellobiitol, was investigated in this study.

The high temperature alkaline degradation of 1,5-anhydrocellobiitol results in the formation of 1,5-anhydro-D-glucitol (80-90%), 1,5:3,6-dianhydro-D-galactitol (ca. 10%), and unidentified products (0-10%) (thought to be small fragments). At 2.5N sodium hydroxide a good mass balance was obtained with the identified products. However, at 0.5N sodium hydroxide a mass deficit (the unidentified products) was encountered. The above product analysis demonstrated that the glycosidic linkage was cleaved at both the glycosyl-oxygen bond (80-90%) and the oxygen-aglycon bond (10-20%).

The addition of a stronger nucleophile (I^-) than hydroxide ion at constant hydroxide ion concentration did not increase the rate of degradation of 1,5-anhydrocellobiitol. Hence, an S_N2 mechanism does not govern the alkaline cleavage of either bond of 1,5-anhydrocellobiitol.

The pseudo-first-order kinetics of the alkaline degradation of 1,5-anhydrocellobiitol in oxygen-free 2.5N sodium hydroxide and 0.5N sodium hydroxide, 2.0F sodium p-toluenesulfonate were investigated between 160 and 180°C. Quantitative gas-liquid chromatography was employed in the analysis. The enthalpy of activation determined for the glycosyl-oxygen bond was ca. 37 kcal./mole at both alkali levels, while that for the oxygen-aglycon bond was ca. 42 kcal./mole at both alkali levels. The above results suggest that

a different mechanism(s) governs each bond cleavage but that the mechanism(s) involved in each bond cleavage are constant over the temperature and alkali range investigated. The very high enthalpy of activation for the oxygen-aglycon bond is indicative of an S_N1 mechanism. There is, however, some question as to the mechanism involved in glycosyl-oxygen bond cleavage.

The increase in rate of cleavage of the oxygen-aglycon bond with increasing ionic strength is indicative of an S_N1 mechanism. The decrease in rate of glycosyl-oxygen bond cleavage with increasing ionic strength suggests an S_N1cB type mechanism.

The effect of hydroxide ion concentration (0.5N and 2.5N sodium hydroxide) was investigated at constant ionic strength at 170°C. The rate of reaction has a significant dependence on hydroxide ion concentration but the order of the reaction with respect to hydroxide ion concentration is a function of hydroxide ion concentration (0.69 at 0.5N NaOH; 0.30 at 2.5N NaOH). This effect was shown to be caused by ionization in the leaving group prior to bond cleavage (lowers leaving ability of leaving group) by investigating the alkali dependence of the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.

The α-linked analog to 1,5-anhydrocellobiitol (1,5-anhydromaltitol), which precludes both the $S_N1cB(2)$ and $S_N1cB(4)$ mechanisms, was subjected to alkaline degradation. The results of this limited investigation suggest that the S_N1 mechanism is a viable route for the alkaline degradation of 1,5-anhydrocellobiitol.

The results of this study indicate that the alkaline degradation of 1,5-anhydrocellobiitol takes place at both the glycosyl-oxygen and oxygen-aglycon bond and that neither bond cleavage is governed by an S_N2 mechanism. Cleavage of the oxygen-aglycon bond is governed by an S_N1 mechanism. The mechanism of cleavage of the glycosyl-oxygen bond is unclear but appears to have characteristics of both S_N1 and S_N1cB mechanisms.

INTRODUCTION

Alkaline degradation of cellulose is an important consideration in the commercial pulping of wood and other cellulosic raw materials. The basic objective of the pulping operation is to obtain the highest possible yield of cellulosic material commensurate with quality considerations. Since all alkaline pulping processes cause at least some degradation of the cellulosic constituents of the wood during the delignification process, a clearer understanding of the complex phenomena of alkaline degradation might allow modification(s) to the process which could reduce the loss of raw material.

ALKALINE DEGRADATION OF CELLULOSE

Alkaline degradation of cellulose may proceed by two pathways. The first pathway is the "peeling" reaction, which will be only briefly described; the second pathway is the alkaline cleavage of glucosidic bonds. The "peeling" reaction has been studied extensively, particularly by Kenner and Richards (1), and has been reviewed by Whistler and BeMiller (2). This reaction proceeds by a stepwise loss of glucose units from the reducing end of the polysaccharide chain until either the polysaccharide is completely degraded, or the reducing end of the polysaccharide rearranges to an alkali-stable metasaccharinic acid via the "stopping" reaction. The "stopping" reaction occurs on the average after 50 to 65 glucose units have been lost via the "peeling" reaction (3), and below 100°C., the "stopping" reaction eventually stabilizes the polysaccharide chain (4). However, above 100°C. and at high pH, the second mode of alkaline degradation, cleavage of glycosidic bonds, becomes significant. Cleavage of glycosidic bonds greatly reduces the average polysaccharide chain length and simultaneously creates new reducing end groups which allows the peeling reaction to become operative. Thus, the cellulose does not become

stabilized to the alkali, and as pulping conditions are approached, cellulose degradation becomes severe with a rapid loss of weight and decrease in the degree of polymerization (5,6).

ALKALINE DEGRADATION OF CELLULOSE MODEL COMPOUNDS

A critical study of the alkaline cleavage of the glucosidic bonds in cellulose is quite difficult because of the inability to precisely define the starting material and the resulting products. Primarily for this reason, most of what is thought to be known about alkaline cleavage of glucosidic bonds in cellulose has been extrapolated or inferred from studies of alkaline degradation of aryl and alkyl glycosides.

ARYL GLYCOPYRANOSIDES

The lability of phenyl β-D-glucopyranoside in aqueous alkali has been known for about 100 years (7). It was only about 25 years ago, however, that McCloskey and Coleman (8) proposed a mechanism to rationalize the rapid cleavage of the glycosidic bond of phenyl β-D-glucopyranoside with concomitant formation of 1,6-anhydro-β-D-glucopyranose in aqueous alkali. The mechanism proposed was based, in part, on the observation that phenyl β-D-glucopyranoside reacts quite rapidly in 1.3N aqueous potassium hydroxide at 100°C. (complete in 9 hr.) while phenyl α-D-glucopyranoside and phenyl 2-O-methyl-β-D-glucopyranoside are essentially stable under these conditions (8).

McCloskey and Coleman's proposed mechanism (8) (M-C mechanism) requires that the C-2 hydroxyl be able to ionize and that the C-2 alkoxy anion thus formed be trans to the aglycon. The M-C mechanism, which is a $S_N1cB(2)$[1]

[1]The $S_N1cB(2)$ notation signifies a unimolecular nucleophilic substitution by the conjugate base of the C-2 hydroxyl.

mechanism (Fig. 1), is envisioned as a rapid, reversible ionization of the C-2 hydroxyl (I → I_a) followed by a rate-limiting, nucleophilic displacement of the aglycon (phenoxide anion) by the trans C-2 alkoxy anion (I_a) to yield 1,2-anhydro-α-D-glucopyranose (II). In phenyl β-D-glucopyranoside the requisite trans diaxial conformation between the C-2 alkoxy anion and the aglycon is achieved in the 1C conformation of the pyranose ring (I_a).

When the resultant 1,2-epoxide is trans to C-6 (as shown in Fig. 1), subsequent intramolecular nucleophilic attack by the C-6 alkoxy anion at C-1 can form 1,6-anhydro-β-D-glucopyranose (III). Alternatively, intermolecular nucleophilic attack by a hydroxide ion at C-1 of 1,2-anhydro-α-D-glucopyranose can presumably yield a reducing sugar (IV) which subsequently degrades in the alkaline medium.

The mode of degradation of the 1,2-epoxide is not critical to the M-C mechanism. However, the high yield of 1,6-anhydro-β-D-glucopyranose [88% (8,10)] suggests that attack by the C-6 alkoxy anion is the dominant route of degradation of 1,2-anhydro-α-D-glucopyranose. When the structure of the glycoside is such that the C-6 alkoxy anion is cis to the resultant 1,2-epoxide, as with phenyl α-D-mannopyranoside (V → VI) or nonexistent, as with phenyl β-D-xylopyranoside (VII → VIII), the reaction products are best described as tars (10) which presumably result from alkaline degradation of an intermediate reducing sugar.

The M-C mechanism has had general utility in predicting which anomer of anomeric phenyl glycopyranosides is more susceptible to alkaline degradation (10) and rationalizing the significant decrease in the reactivity of trans-1,2 oriented phenyl 2-O-methyl-glycopyranosides relative to the unsubstituted

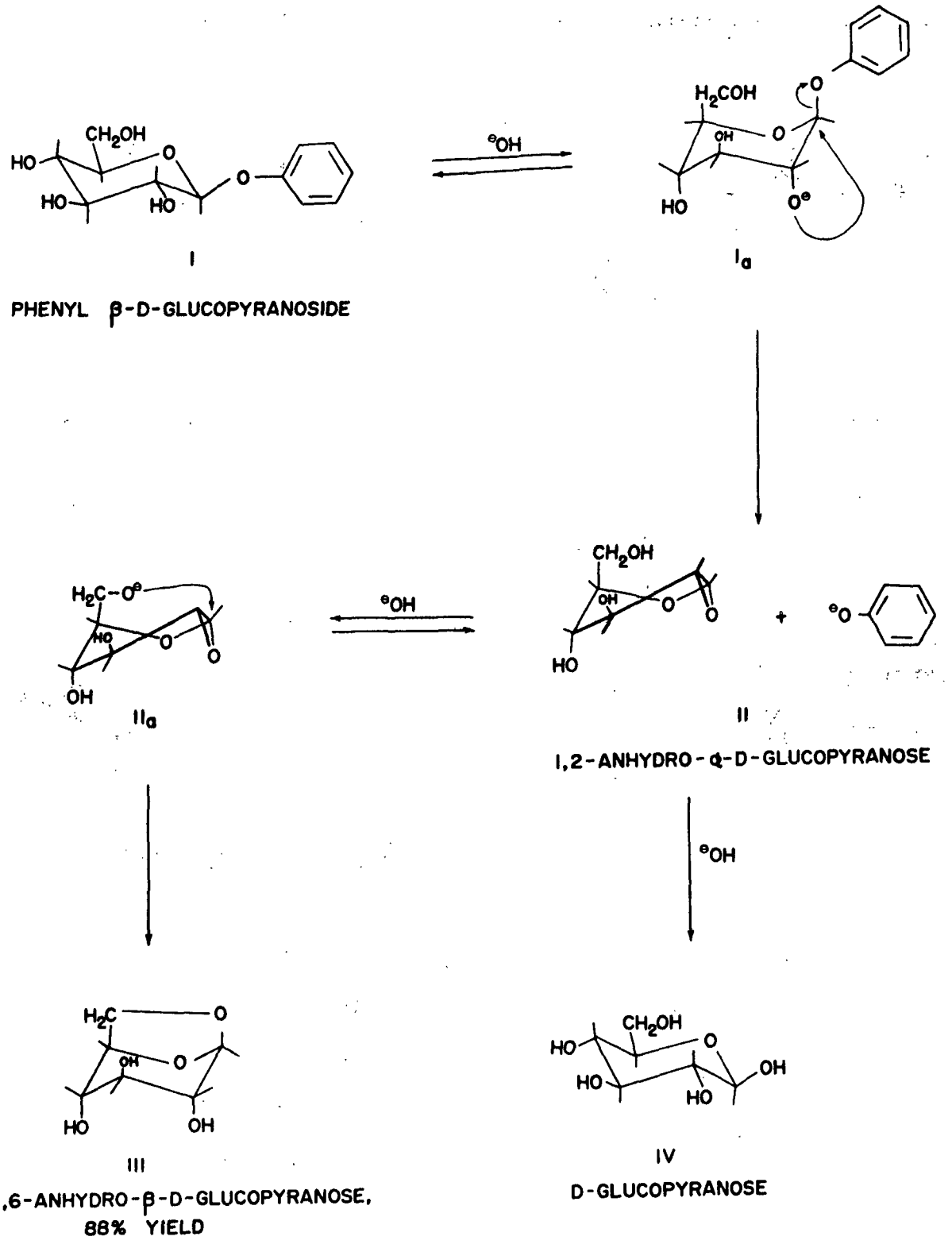
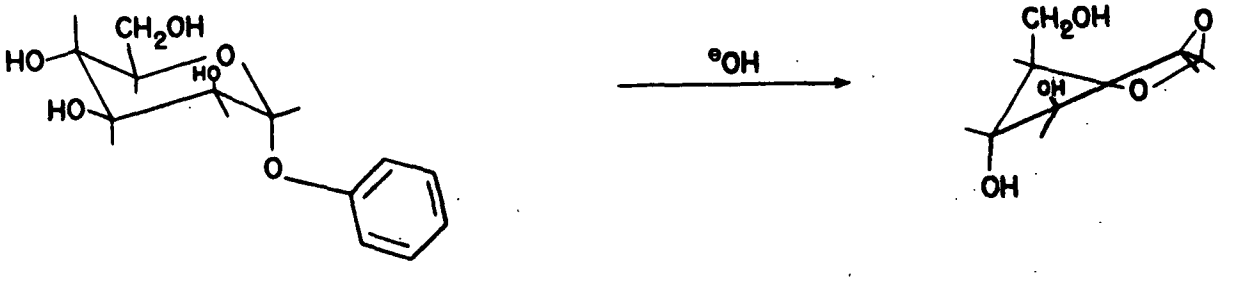


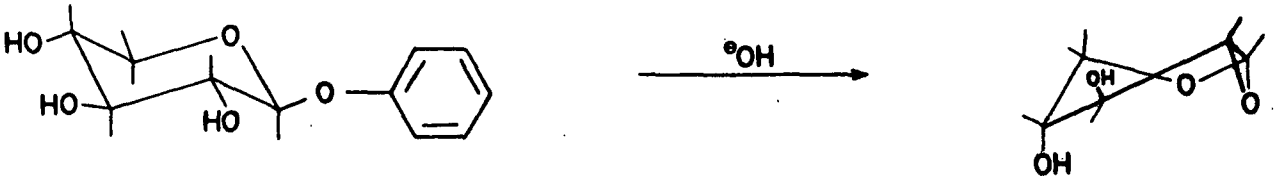
Figure 1. Proposed Mechanism for the Alkaline Degradation of Phenyl β-D-glucopyranoside (8,9)

parent glycosides (11,12). However, the alkaline degradation of phenyl glycosides cannot be successfully rationalized on the basis of any single mechanism (9).



V
Phenyl α-D-mannopyranose

VI
1,2-Anhydro-β-D-mannopyranose



VII
Phenyl β-D-xylopyranoside

VIII
1,2-Anhydro-α-D-xylopyranose

Phenyl β-D-mannopyranoside (IX) (cis-1,2 configuration) reacts in aqueous alkali at a rate comparable to that observed for the trans-1,2-mannoside. In addition, a substantial yield (57%) of 1,6-anhydro-β-D-mannopyranoside (XI) is obtained (10). A mechanism (9) (Fig. 2) which rationalizes the observed formation of the anhydrosugar (XI) proposes an S_N1 type heterolysis of the glycosidic bond to form a D-mannopyranosyl cation (X) which then undergoes nucleophilic attack by either the C-6 alkoxy anion to form XI or a hydroxide ion to yield the reducing sugar, XII, which subsequently degrades.

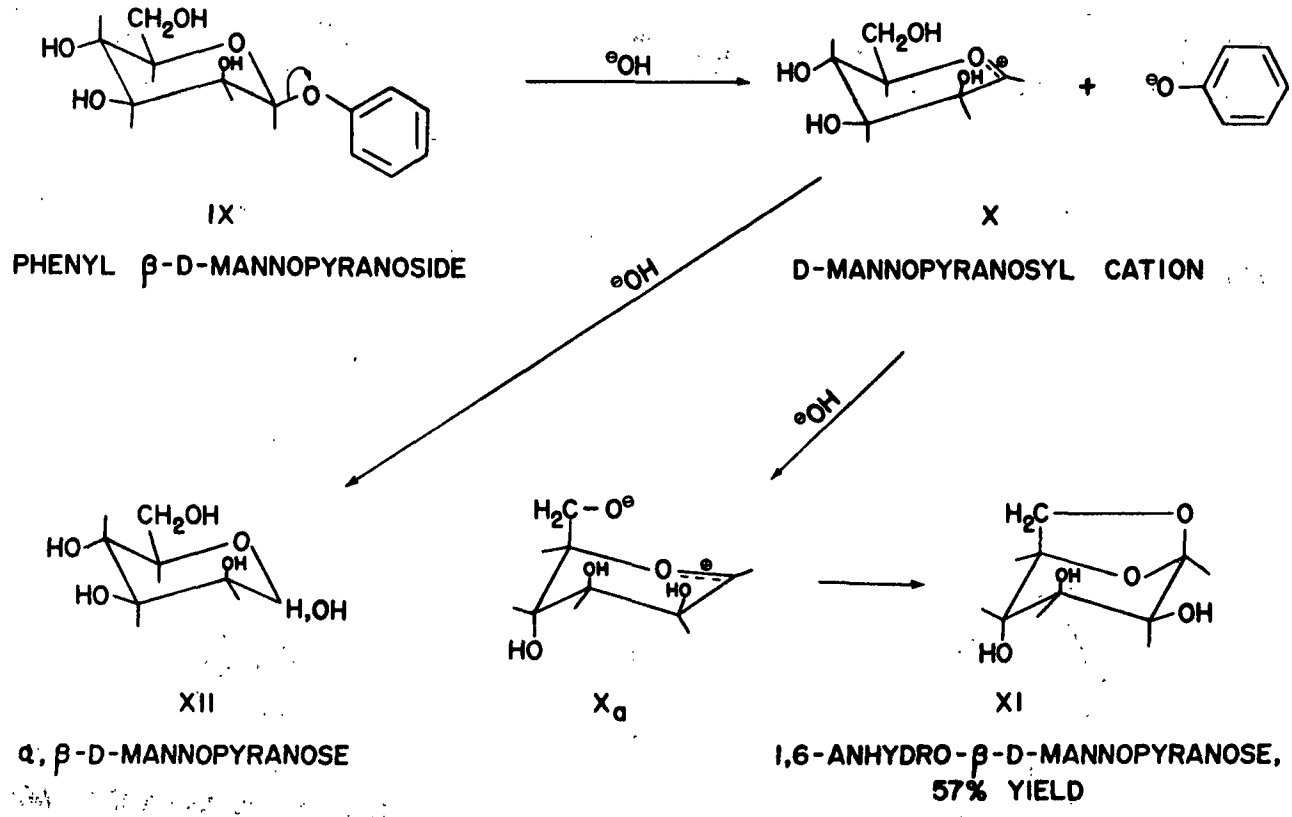


Figure 2. Proposed Mechanism for the Alkaline Degradation of Phenyl β-D-Mannopyranoside (9)

Alternatively, Capon (13) has proposed (Fig. 3) that the C-4 alkoxy anion of phenyl β-D-mannopyranoside, IX_a, displaces the aglycon to yield 1,4-anhydro-α-D-mannopyranose (XIII) [an $S_N1cB(4)$ mechanism]. Direct attack by the C-6 alkoxy anion at C-1 of XIII to form 1,6-anhydro-β-D-mannopyranose (XI) is not likely for stereochemical reasons. Thus, the 1,4-anhydro intermediate (XIII) must first form the D-mannopyranosyl cation (X) which reacts as discussed previously (Fig. 2).

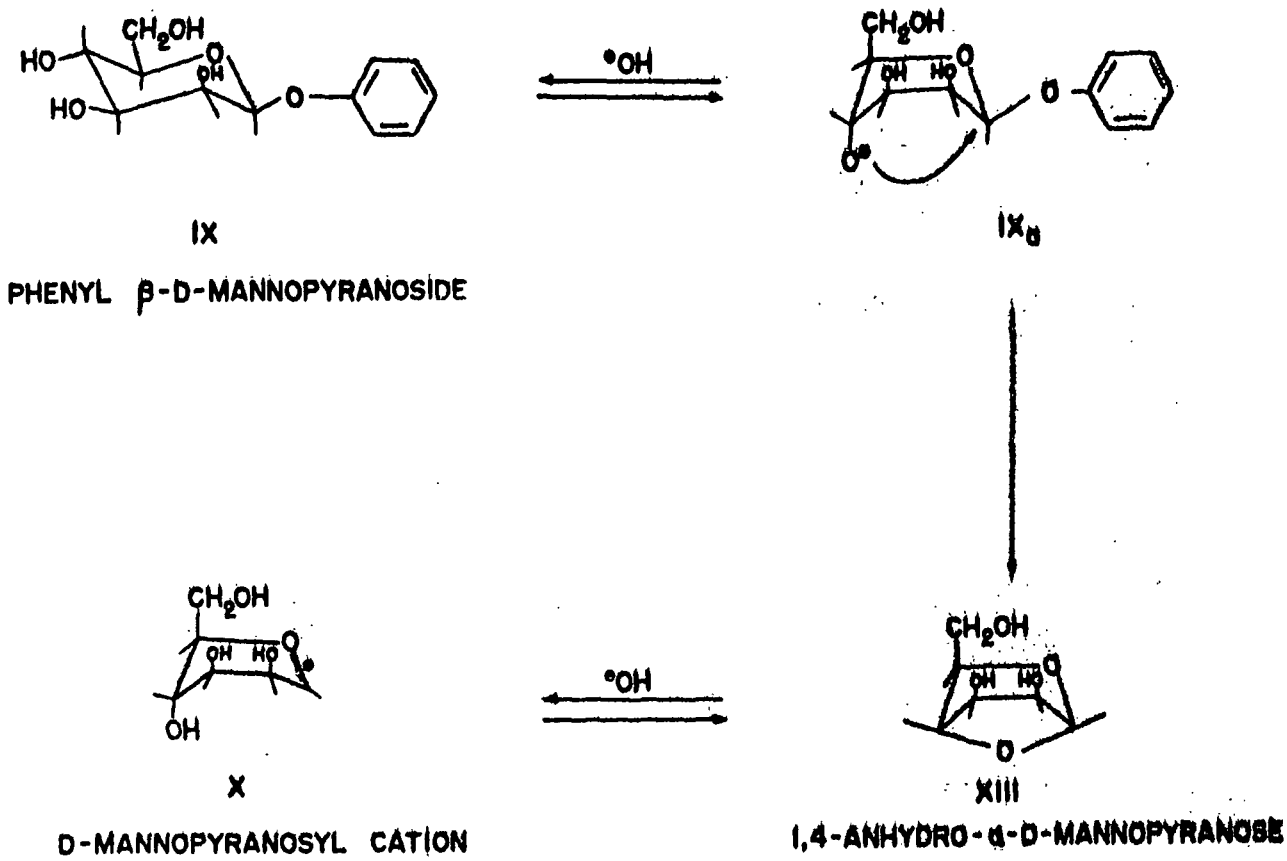


Figure 3. Proposed Mechanism for the Formation of D-Mannopyranosyl Cation from Phenyl β-D-Mannopyranoside (13)

Phenyl α-D-galactopyranoside (cis-1,2 configuration) reacts very slowly (3×10^{-3} times the rate of the trans-1,2 glycoside) in 2.6N potassium hydroxide at 100°C. to give 1,6-anhydro-β-D-galactopyranose in 85% yield (10). While it could be argued that such a large depression in the rate of degradation vindicates the prediction of stability on the basis of the M-C mechanism, an 85% yield of the anhydro sugar cannot be overlooked. The mechanism proposed (8) to rationalize the conversion of phenyl α-D-galactopyranoside (XIV) to 1,6-anhydro-β-D-galactopyranose (XV) (Fig. 4) involves an intramolecular nucleophilic attack by the C-6 alkoxy anion at C-1 to displace the aglycon, i.e., an

$S_N1cB(6)$ mechanism. Phenyl α-D-glucopyranoside does not undergo an analogous reaction (i.e., is stable under these reaction conditions); however, Capon (13) states that the formation of 1,6-anhydro-β-D-galactopyranose (XV) would be expected to occur more readily than the formation of 1,6-anhydro-β-D-glucopyranose (III) since in the former the C-4 hydroxyl group is equatorial while in the latter it is axial.

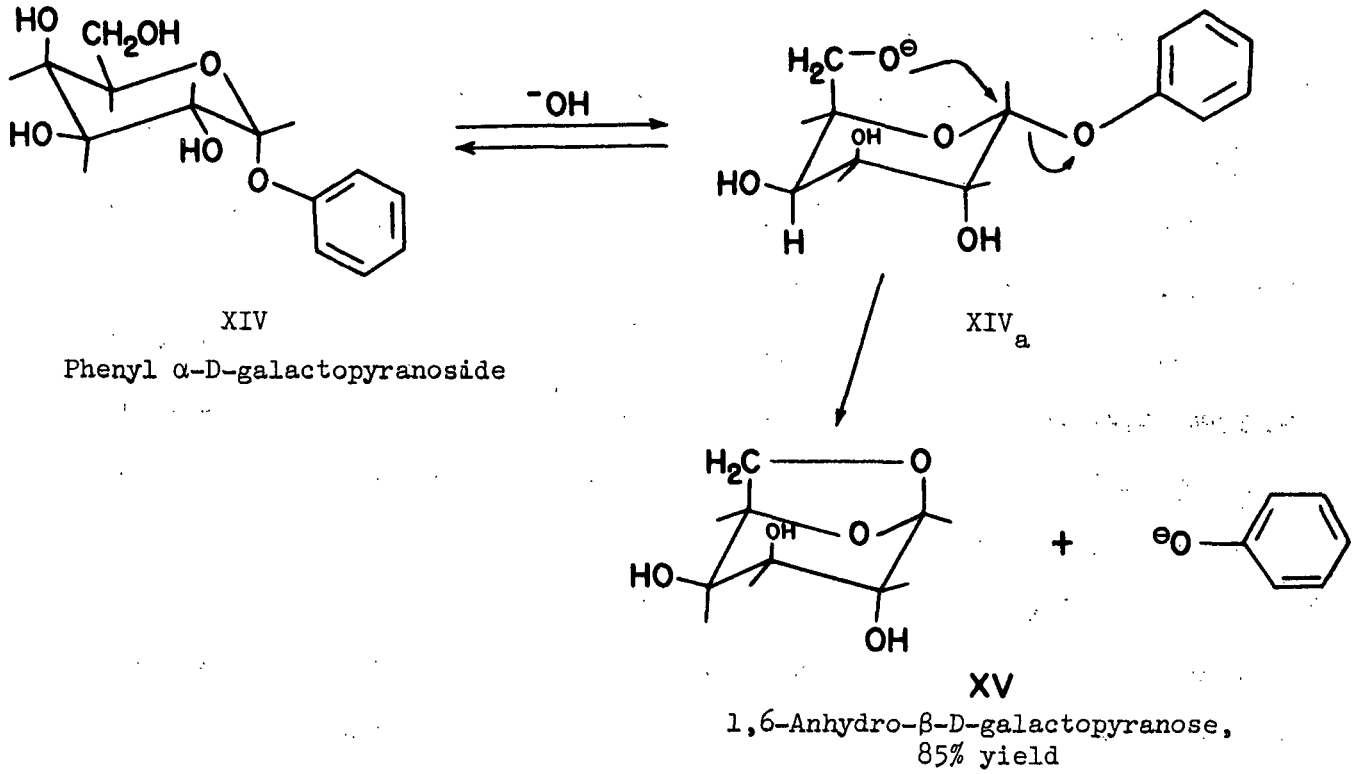


Figure 4. Proposed Mechanism for the Alkaline Degradation of Phenyl α-D-galactopyranoside (8)

It would be expected that increasing the "leaving ability" of the aglycon would increase the rate of degradation of aryl glycopyranosides regardless of the type of mechanism operating. "Leaving ability" is a function of the ability of the fragmenting species to stabilize or delocalize the pair of electrons acquired through bond cleavage. Thus, the "leaving ability" of the aglycon should be inversely proportional to the basicity of the corresponding

phenoxide species (14). Dyferman and Lindberg (15) observed a linear relationship in the predicted direction, between the basicity of a series of substituted phenoxides and the rate of degradation of the corresponding phenyl β-D-glucopyranosides.

It appears that the yield of 1,6-anhydro-β-D-glucopyranose (III) decreases as the "leaving ability" of the phenyl aglycon increases, i.e., an 88% yield of III is obtained from phenyl β-D-glucopyranoside while only a 60% yield of III is obtained from both o- and p-nitrophenyl β-D-glucopyranoside (10). In addition, both o- and p-nitrophenyl α-D-glucopyranosides (cis-1,2 configuration) degrade rapidly in alkali (rate comparable to β-anomer) (10). Several workers (8,9) have interpreted these observations as suggesting that the reaction mechanism shifts toward an S_N1 type mechanism as the "leaving ability" of the aglycon increases. However, recent work (15) has shown that the sensitivity of p-nitrophenyl α-D-glucopyranoside (XVI) to alkaline degradation is the result of an intramolecular nucleophilic attack by the C-2 alkoxy anion (XVI_a-XVI_b) on the aromatic ring (Fig. 5). This results in the p-nitrophenoxyl group migrating to C-2 (XVII). A similar migration to C-3 (XVIII) allows the sugar to degrade via a peeling type reaction, i.e., the sugar rearranges to a saccharinic acid with β-alkoxy elimination of the 3-O-(p-nitrophenyl) group. This type of mechanism is also reportedly operative at a lower rate in the β-anomer (15). Thus, some doubt is thrown on the suggestion of a mechanistic shift toward an S_N1 mechanism as the "leaving ability" of the aglycon increases.

While the mechanism proposed by McCloskey and Coleman is consistent with much of the alkaline degradation data observed for phenyl glycopyranosides, other mechanisms obviously also play a role in the alkaline degradation of some phenyl glycopyranosides.

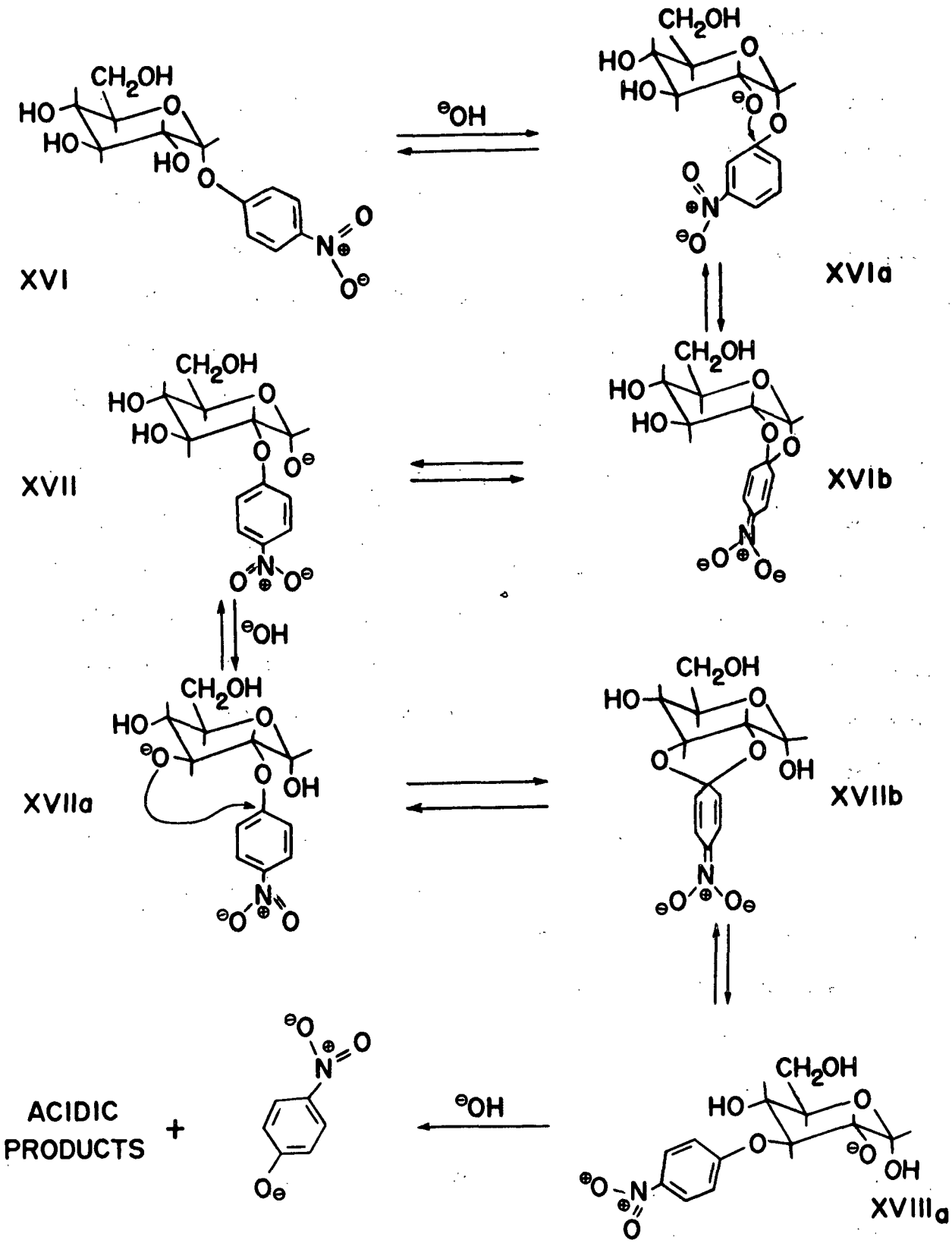


Figure 5. Proposed Mechanism for the Alkaline Degradation of p-Nitrophenyl α-D-Glucopyranoside (16)

ALKYL GLYCOPYRANOSIDES

The reaction conditions required to give reasonable rates of alkaline degradation of alkyl glycopyranosides are considerably more drastic (2.5N sodium hydroxide, 170°C.) than those required for the alkaline degradation of aryl glycopyranosides (1.3N potassium hydroxide, 100°C.). As a result, characterization of these reactions is complicated because the anticipated products, e.g., 1,6-anhydroglucopyranoses and reducing sugars, are degraded much more rapidly under these conditions than the alkyl glycopyranosides (13,17).

The M-C mechanism was initially extended to alkaline degradation of alkyl glycopyranosides by Lindberg (18). More recently Brooks (19) and Best (20) concluded that their data on the alkaline degradation of methyl β-D-glucopyranoside and methyl β-cellobioside, respectively, were consistent with the M-C mechanism. However, evidence that other mechanisms may be operative in the alkaline degradation of alkyl glycopyranosides has been pointed out by Lindberg, et al. (21,22).

If the M-C mechanism is the primary pathway for alkaline degradation of alkyl glycopyranosides with a trans-1,2 configuration, precluding direct participation by the alkoxy anion, e.g., cis-1,2 configuration or 2-O-methyl substitution should decrease the rate of reaction significantly. For a series of methyl D-glucopyranosides investigated in 10% sodium hydroxide at 170°C. (21,22), those compounds with a trans-1,2 configuration reacted only 3-10 times faster than those with a cis-1,2 configuration (Table I). Also, methyl 2-O-methyl-β-D-glucopyranoside reacts at about one-half the rate reported for methyl β-D-glucopyranoside (Table I). Thus, anchimeric assistance, if operative in the alkyl glycosides with a trans-1,2 configuration, appears to be slight (13).

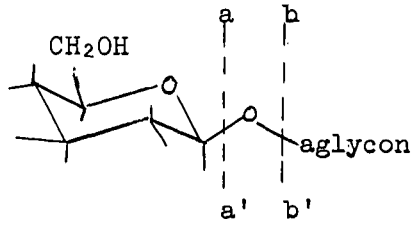
TABLE I

DEGRADATION RATES OF VARIOUS METHYL GLUCOPYRANOSIDES IN 10% AQUEOUS SODIUM HYDROXIDE AT 170°C.

Methyl Glycopyranoside of	$k_d \times 10^6$, sec.$^{-1}$ *trans* config.	Anomer	Ref.	$k_d \times 10^6$, sec.$^{-1}$ *cis* config.	Anomer	Ref.
D-Glucose	1.66	β	22	0.64	α	22
	2.29		20	0.85		23
D-Galactose	3.64	β	21	0.62	α	21
D-Mannose	1.79	α	21	0.70	β	21
D-Xylose	3.71	β	21	0.77	α	21
L-Arabinose	6.39	α	21	0.64	β	21
2-*O*-Methyl-D-glucose	0.77	β	22	0.51	α	22

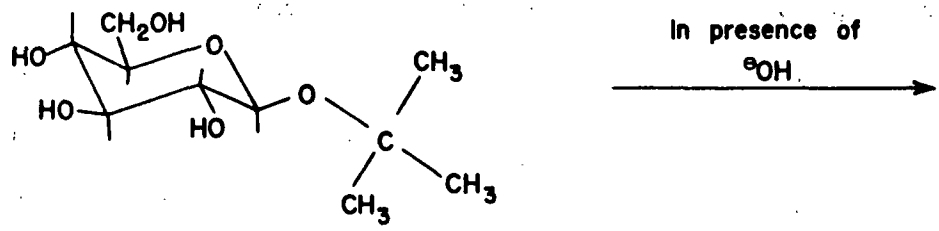
Janson and Lindberg (22) have also studied the effect of the alkyl group on the rate of alkaline degradation of alkyl β-D-glucopyranosides. Based on the "leaving ability" of the alkoxy anions, the rate of alkaline degradation of the corresponding alkyl β-D-glucopyranosides would be expected to decrease in the order methyl > ethyl > iso-propyl > t-butyl. However, the observed order of the rate of degradation is opposite to the expected order, i.e., methyl < ethyl < iso-propyl < t-butyl. Lindberg did not propose a mechanism to resolve these observations. Recent work (20) has indicated that some cleavage of the oxygen-aglycon bond[2] (11%) is observed with a methyl aglycon. One possible explanation for this is that bond cleavage occurs with formation of a methyl cation[3]. Since a methyl aglycon would generate the least stable alkyl cation, while a t-butyl aglycon would generate the most stable cation, the observed order of degradation rates is consistent with heterolysis of the oxygen-aglycon bond (e.g., Fig. 6). The mechanism could feasibly shift from a "predominantly" M-C mechanism to a "predominantly" alkyl cation mechanism as

[2]The glycosyl-oxygen bond is intersected by a-a', while the oxygen-aglycon bond is intersected by b-b'.

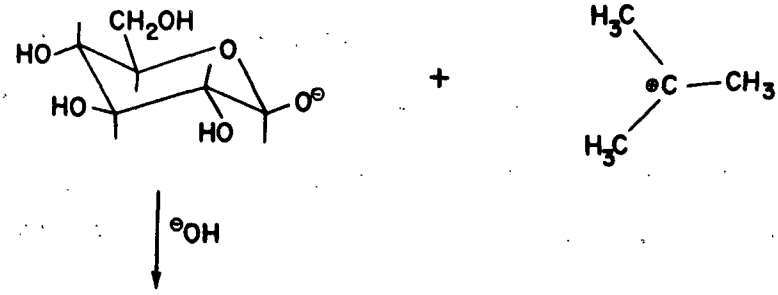


[3]An alternate explanation for oxygen-aglycon bond cleavage involves direct nucleophilic attack by hydroxide ion (S_N2 mechanism) at the aglycon to displace the glucopyranosyloxy anion. However, Streitwieser (24) indicates that the average relative rates of reaction for alkyl derivatives via an S_N2 mechanism would be methyl, 30; ethyl, 1; iso-propyl, 0.025; and t-butyl, nil. Therefore, an S_N2 attack by hydroxide on the aglycon of an alkyl glucopyranoside would be a viable mechanism only for the alkaline degradation of methyl β-D-glucopyranoside and could not explain the observed relative reactivities in the series of alkyl β-D-glucopyranosides investigated.

the transition from methyl β-D-glucopyranoside to t-butyl β-D-glucopyranoside is made.



t-Butyl β-D-glucopyranoside



Acidic products

Figure 6. Possible Mechanism for the Alkaline Degradation of t-Butyl β-D-Glucopyranoside

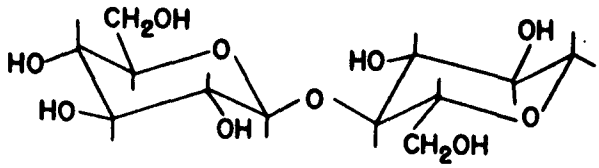
Recent work by Robins (23) has led to a proposed $S_N1cB(6)$ mechanism for the alkaline degradation of methyl α-D-glucopyranoside in which the C-6 alkoxy anion attacks C-1 thereby producing 1,6-anhydro-β-D-glucopyranose as a primary degradation product. Since this mechanism was originally proposed by McCloskey and Coleman for the alkaline degradation of phenyl α-D-galactopyranoside (8) (Fig. 4), it could also be operative in the alkaline degradation of methyl α-D-galactopyranoside. Similarly, Capon's proposed mechanism for the alkaline degradation of phenyl β-D-mannopyranoside (Fig. 3) could be operative in the alkaline degradation of methyl β-D-mannopyranoside, methyl

β-L-arabinoside, and methyl 2-O-methyl β-D-glucoside as the possibility of the formation of 1,4-anhydroglycopyranoses in the alkaline degradation of these compounds has not been investigated. Since all of the mechanisms mentioned are of the S_N1cB type, as is the M-C mechanism, the differences observed in the rate of alkaline degradation of various methyl glycopyranosides could be due to the slightly different nucleophiles, ring strain involved in the transition state, and entropy effects encountered in the different glycosides.

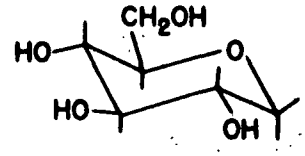
The alkaline hydrolysis of methyl α-D-xylopyranoside, however, must proceed by a S_N1 or possibly S_N2 mechanism as no S_N1cB mechanism can be proposed for this compound. The possibility of the C-2 alkoxy anion being involved in a nucleophilic attack on the central carbon atom of the alkyl aglycon by a mechanism somewhat analogous to that proposed for the alkaline degradation of p-nitrophenyl α-D-glucopyranoside (Fig. 5) is considered unlikely because of stereochemical considerations.

DIRECTION OF THIS RESEARCH

From the preceding discussion it should be apparent that a number of mechanisms is possible for alkaline degradation of glycosidic linkages. This study is concerned with the mechanism(s) involved in the alkaline degradation of 1,5-anhydrocellobiitol in oxygen-free, aqueous alkali at high temperatures. 1,5-Anhydrocellobiitol [1,5-anhydro-4-O-(β-D-glucopyranosyl)-D-glucitol] (XIX) is a relatively simple model compound for cellulose in that it has only one glycosidic linkage and no reducing end group. It should be noted, however, that the aglycon [1,5-anhydro-D-glucitol (XX)] should be a much closer approximation to a second glucosyl ring than is a simple alkyl group. Also, at least one of the expected degradation products, 1,5-anhydro-D-glucitol (XX), should be stable to hot alkali since ring closure is via an ether linkage.



1,5-Anhydrocellobiitol, XIX



1,5-Anhydro-D-glucitol, XX

In this investigation, the effects of varying hydroxide ion concentration at constant ionic strength, varying ionic strength at constant hydroxide ion concentration, a strong nucleophile, and steric factors on the alkaline degradation of 1,5-anhydrocellobiitol at 170°C. were studied. The temperature dependence of the reaction was also determined (160-180°C.). Organic reactant concentrations of ca. 0.01M were employed so that the alkali (0.05N, 1.0N, 1.5N, and 2.5N sodium hydroxide) was always present in a large excess in order that pseudo-first-order kinetic methods were applicable. The above conditions are similar to commercial pulping conditions in terms of temperature and alkali levels.

RESULTS

ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL

PRELIMINARY RESULTS

It was shown that the reactant and nonionic products in the alkaline degradation of 1,5-anhydrocellobiitol could be determined with suitable accuracy and precision (±2%) by quantitative gas-liquid chromatographic (GLC) analysis of the acetylated reaction mixture.

Preliminary investigations demonstrated that the oxygen-free alkaline degradation of 1,5-anhydrocellobiitol was not affected (catalyzed) by a stainless steel reaction vessel as compared to a teflon vessel. Thus, teflon lining of the reactor was unnecessary and a batch-type reactor was fabricated of Type 316 stainless steel. The reactor was outfitted so that the temperature of the reaction mixture could be continuously monitored and samples withdrawn at desired intervals.

It was also shown that the expected primary degradation product, 1,5-anhydro-D-glucitol, was stable in 2.5N sodium hydroxide at 170°C. for at least 168 hr. and in 0.5N sodium hydroxide, 2.0F sodium p-toluenesulfonate[4] at 170°C. for at least 471 hr.

PRODUCT IDENTIFICATION

As was expected, the primary product of the alkaline degradation of 1,5-anhydrocellobiitol is 1,5-anhydro-D-glucitol (XX; AG). A second "unexpected"

[4]Sodium p-toluenesulfonate was chosen as the salt used to maintain constant ionic strength because of its low redox potential and nucleophilicity. The nucleophilicity of sodium p-toluenesulfonate is <1 on the Swain scale (25).

product 1,5:3,6-dianhydro-D-galactitol (XXI; DAG), was also formed. The identification of the latter compound was made by GLC-mass spectrometry and by comparing the NMR and IR spectra of the degradation product and an authentic sample of 1,5:3,6-dianhydro-D-galactitol.

The stability of 1,5:3,6-dianhydro-D-galactitol to the reaction conditions was not demonstrated directly. However, the ratio of 1,5-anhydro-D-glucitol (demonstrated to be stable) to 1,5:3,6-dianhydro-D-galactitol in the product mixture was constant at long reaction times; thus, it was inferred that 1,5:3,6-dianhydro-D-galactitol was stable to hot alkali.

Several other products were also identified in the product mixture. 1,6-Anhydro-β-D-glucopyranose (III; L) was present but the concentration at any given time was relatively low since under the reaction conditions it degraded quite rapidly. 1,5-Anhydro-D-gulitol (XXII) and 1,5-anhydro-D-galactitol (XXIII) were identified in the product mixture by GLC and paper chromatography.

A portion of the products could not be detected by GLC and are presumed to be either ionic in nature or small fragments which could not be resolved from the solvent front by the type of column needed for analysis of the identified products. The amount of these product(s) was determined by the difference between the moles of 1,5-anhydrocellobiitol degraded and the moles of identified products formed from the 1,5-anhydro-D-glucitol portion of the reactant molecule.

KINETIC DESCRIPTION OF THE REACTION

Pseudo-First-Order Degradation of 1,5-Anhydrocellobiitol

1,5-Anhydrocellobiitol (0.01 or 0.02M) was allowed to react in oxygen-free aqueous alkali (0.5-2.5N NaOH) for 4 to 54 hr. at 160-180°C. The rate

of disappearance of 1,5-anhydrocellobiitol under these conditions was described by Equation (1).

$$dR/dt = -k\, R^{a}\, [^{\ominus}OH]^{b} \qquad (1)$$

where k = specific rate constant, $sec.^{-1}$,

R = concentration of reactant at time t, mole/liter,

$[^{\ominus}OH]$ = concentration of hydroxide ion, mole/liter,

a = constant, initially assumed to be 1.0, and

b = constant.

Integration yields:

$$\ln(R/R_{o}) = -k\, [^{\ominus}OH]^{b}\, t \qquad (2)$$

where R_{o} = concentration of reactant at $t = 0$, mole/liter.

Since hydroxide ion was present in large excess, its concentration was essentially constant and

$$\ln(R/R_{o}) = -k_{r}t \qquad (3)$$

where $k_{r} = k[^{\ominus}OH]^{b}$ = pseudo-first-order rate constant for the degradation of reactant, $sec.^{-1}$, and

$R/R_{o} = X_{r,t}$ = mole fraction of reactant at time t.

Pseudo-first-order rate constants for the disappearance of reactant were calculated by the method of least squares according to Equation (3). The linearity of the data when plotted according to Equation (3) indicated the reaction was first-order with respect to reactant, i.e., $a = 1.0$ (see Fig. 7). In addition, the kinetic order with respect to 1,5-anhydrocellobiitol was calculated as 1.1 from the pseudo-first-order alkaline degradation rates at two 1,5-anhydrocellobiitol concentrations (0.01 and 0.02M) by the half-life method (26).

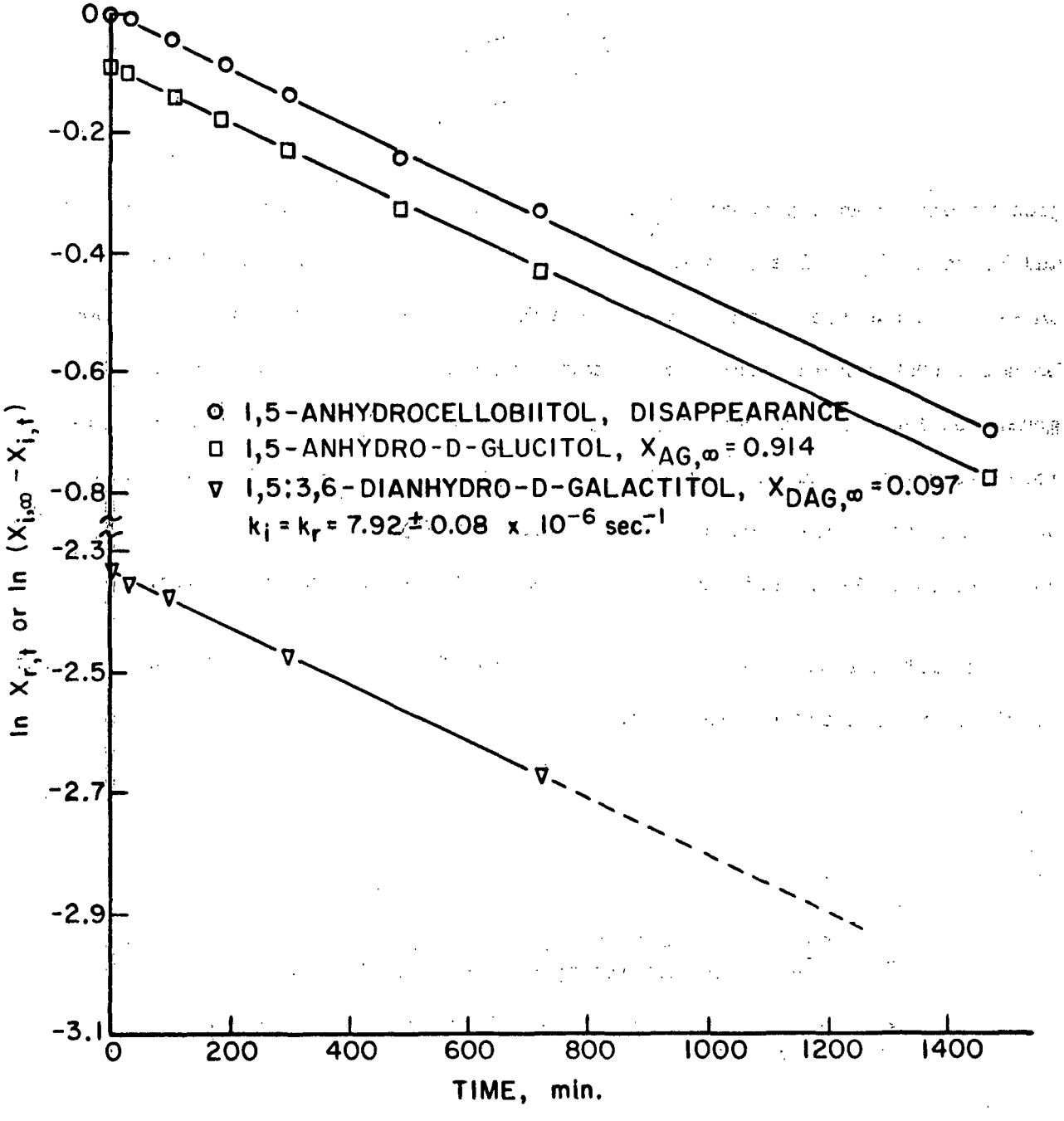
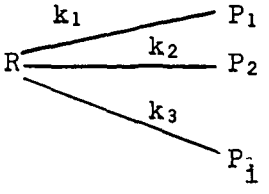


Figure 7. Kinetic Plot for the Alkaline Degradation of 1,5-Anhydrocellobiitol in 2.5N NaOH at 170°C. (Run b)

Mathematical Description of Parallel-First-Order Kinetics

Parallel first-order kinetics where the reactant (R)



goes to one or more products (P_i) has been described mathematically by Frost and Pearson (26). The constants generated by use of simplified forms of these equations are valuable for a consolidated data presentation. It should be noted that simple molar stoichiometry is maintained only if the products generated from the aglycon (1,5-anhydro-D-glucitol) portion of the reactant molecule during alkaline degradation are considered in the parallel-first-order analysis. The products arising from the glycosyl portion of the molecule could be considered in a similar analysis if they were stable.

The integrated form of the rate equation for the disappearance of reactant is given by Equation (4) [see Equation (3)].

$$\ln X_{r,t} = -k_r t \qquad (4)$$

where $X_{r,t}$ = mole fraction of reactant at time t,

$k_r = \Sigma k_i$ = pseudo-first-order specific rate constant for reactant disappearance, $sec.^{-1}$, and

k_i = pseudo-first-order specific rate constant for the formation of product i, $sec.^{-1}$.

Appearance of each product is described by Equation (5):

$$\ln(X_{i,\infty} - X_{i,t}) = -k_r t + \ln X_{i,\infty} \qquad (5)$$

where $X_{i,t}$ = mole fraction of product i at time t, and

$X_{i,\infty}$ = $X_{i,t}$ at completion (the relative proportion of product i formed),

in this system
$$X_{i,t} = C_{i,t}/C_{r_o} \tag{6}$$

and
$$X_{i,\infty} = C_i/(C_{r_o} - C_{r,t}) \tag{7}$$

where $C_{i,t}$ = concentration of product i in the reaction mixture at time t, mole/liter,

C_{r_o} = concentration of reactant at t = 0, mole/liter, and

$C_{r,t}$ = concentration of reactant at time t, mole/liter.

The value of each individual rate constant, k_i, can be calculated from Equation (8):

$$k_i = k_r X_{i,\infty}. \tag{8}$$

Thus, a complete description of the parallel-first-order kinetics is given by k_r and $X_{i,\infty}$ as any other quantity can be calculated from these quantities and Equations (4)-(8). A typical plot for the disappearance of reactant and appearance of products is shown in Fig. 7. The parallel nature of the curves in Fig. 7 is further evidence that the alkaline degradation of 1,5-anhydrocellobiitol was first-order.

An inherent difficulty resulting from the use of Equation (7) to calculate $X_{i,\infty}$ was the unavoidable scatter in the values obtained due to the short reaction times involved (degradations were not monitored beyond about 30% reaction). Thus, the value of the pseudo-first-order rate constant for product appearance, k_i, which was calculated from the $X_{i,\infty}$ obtained from Equation (7) and k_r using

Equation (8), also exhibited undesirable scatter. For this reason, an alternate form of Equation (5) was used to calculate k_i directly (26):

$$C_{i,t} - C_{i_o} = (k_i C_{r_o}/k_r)[1 - \exp(-k_r t)] \qquad (9)$$

where C_{i_o} = concentration of product i at $t = 0$[5], mole/liter.

A typical plot for the appearance of products according to Equation (9) is shown in Fig. 8. The slope of the curve which was determined by the method of least squares is equal to k_i. The value for $X_{i,\infty}$ was then calculated from k_i and k_r according to Equation (8).

Kinetic Description of the Production of 1,6-Anhydro-β-D-glucopyranose

The determination of the rate of formation of 1,6-anhydro-β-D-glucopyranose (levoglucosan) during the alkaline degradation of a suitable disaccharide reactant was complicated by the rather severe alkali lability of levoglucosan. The production of levoglucosan can be diagrammed as:

$$R \xrightarrow{k_r} \text{total products formed}$$

$$R \xrightarrow{k_{fL}} \text{levoglucosan} \xrightarrow{k_{dL}} \text{acidic products}$$

thus

$$dL/dt = k_{fL}R - k_{dL}L \qquad (10)$$

where L = concentration of levoglucosan at time t, mole/liter,

k_{fL} = pseudo-first-order rate constant for the formation of levoglucosan, $sec.^{-1}$,

[5]Products could potentially be present at zero time which was chosen to be some short time (<1% reaction) after the reactor system had come to the desired temperature.

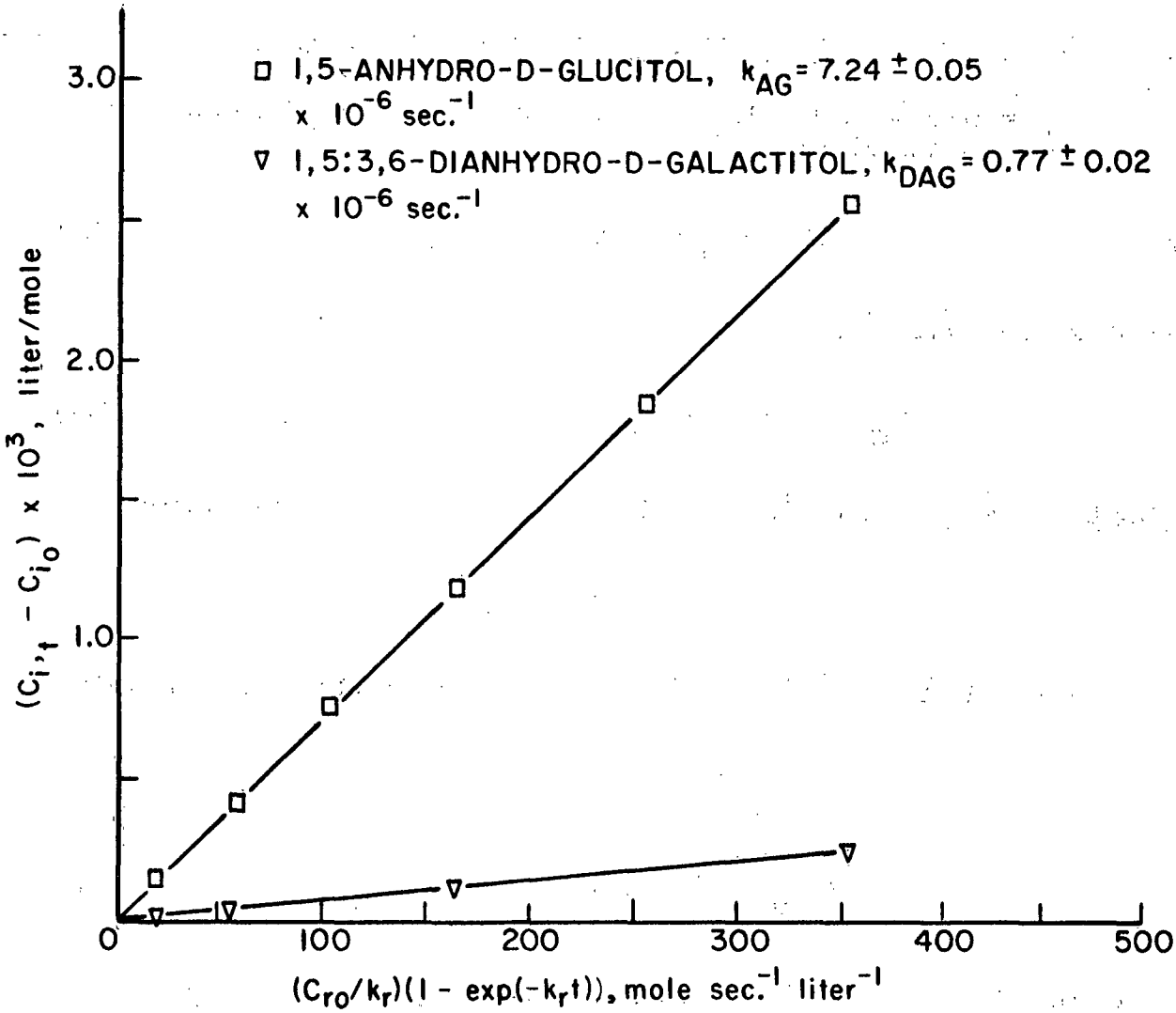


Figure 8. Determination of k_i for the Alkaline Degradation of 1,5-Anhydrocellobiitol in 2.5N NaOH at 170°C. (Run b).

k_{dL} = pseudo-first-order rate constant for the alkaline degradation of levoglucosan, $sec.^{-1}$, and

R = concentration of reactant at time t, mole/liter.

Since
$$R = R_o \exp(-k_r t) \tag{11}$$

where R_o = concentration of reactant to $t = 0$, mole/liter, and

k_r = pseudo-first-order rate constant for the alkaline degradation of the reactant, $sec.^{-1}$,

then
$$dL/dt + k_{dL}L = k_{fL}R_o \exp(-k_r t) \tag{12}$$

integration and rearrangement gives:

$$L = k_{fL}R_o \exp(-k_r t)/(k_{dL} - k_r) + C \exp(-k_{dL}t). \tag{13}$$

Setting $L = L_o$ at $t = 0$, the constant C in Equation (13) can be evaluated as:

$$C = L_o - k_{fL}R_o/(k_{dL} - k_r) \tag{14}$$

which when substituted in Equation (13) and rearranged yields Equation (15):

$$L - L_o \exp(-k_{dL}t) =$$

$$[k_{fL}R_o/(k_{dL} - k_r)][\exp(-k_r t) - \exp(-k_{dL}t)]. \tag{15}$$

Determination of k_{dL} independently (Table IX) allowed calculation of k_{fL} as the slope of the curve generated by the data plotted according to Equation (15) (Fig. 9) and evaluated by the method of least squares.

EFFECT OF VARYING HYDROXIDE ION CONCENTRATION AT CONSTANT IONIC STRENGTH

The pseudo-first-order rate constants which were determined for the alkaline degradation of 1,5-anhydrocellobiitol at 170°C. in varying hydroxide

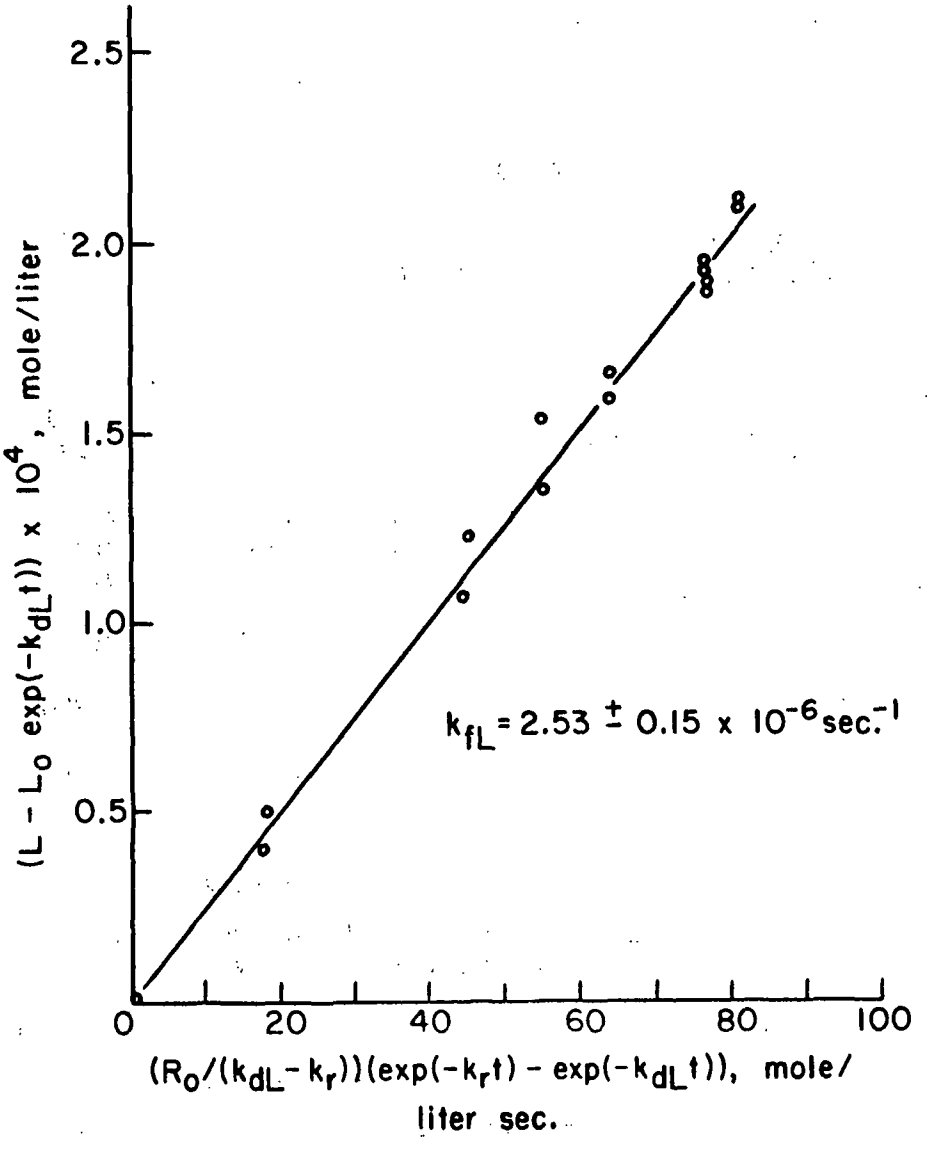


Figure 9. Determination of the Specific Rate Constant for the Formation of 1,6-Anhydro-β-D-glucopyranose in the Alkaline Degradation of 1,5-Anhydrocellobiitol in 2.5N NaOH at 170°C. (Run b)

ion concentration (2.5 to 0.5N) at constant ionic strength (2.5F) are shown in Table II. The rate of degradation increased as the hydroxide ion concentration increased, but the relationship of the degradation rate to hydroxide ion concentration was nonlinear (Fig. 10) and represented only a 1.8 to 2.1-fold increase for a fivefold increase in hydroxide ion concentration.

TABLE II

EFFECT OF VARYING HYDROXIDE ION CONCENTRATION AT CONSTANT IONIC STRENGTH ON THE ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) AT 170°C.

NaOH, N	NaTOS, F	$k_r \times 10^6$, $sec.^{-1}$	$X_{AG,\infty}$	$X_{DAG,\infty}$	$X_{UI,\infty}$ [d]	$X_{L,\infty}$ [e,f]
2.5[a]	0.0	7.99 ± 0.11	0.905	0.101	0.0	0.33
2.5[b]	0.0	7.92 ± 0.08	0.914	0.097	0.0	0.32
2.5[c]	0.0	7.75 ± 0.11	0.957	0.102	0.0	0.33
1.5	1.0	6.74 ± 0.12	0.924	0.105	0.0	0.33
1.0	1.5	5.84 ± 0.11	0.856	0.098	0.046	0.31
0.5	2.0	4.38 ± 0.11	0.801	0.091	0.108	0.26

[a,b,c] Individual reactions are similarly labeled in Appendix IV.

[d] The mole fraction of unidentified products (UI) is determined by the difference, $1.00 - (X_{AG,\infty} + X_{DAG,\infty})$; negative values are reported as 0.0.

[e] The appearance of 1,6-anhydro-β-D-glucopyranose is not included in the mass balance which generates $X_{UI,\infty}$.

[f] The value $X_{L,\infty}$ is hypothetical in that it represents the amount of 1,6-anhydro-β-D-glucopyranose which would be present if it were stable, since in reality no 1,6-anhydro-β-D-glucopyranose remains at infinite time. This is a legitimate use of the notation, however, in that $X_{i,\infty}$ also represents the proportion or mole fraction of product (levoglucosan) formed during the reaction.

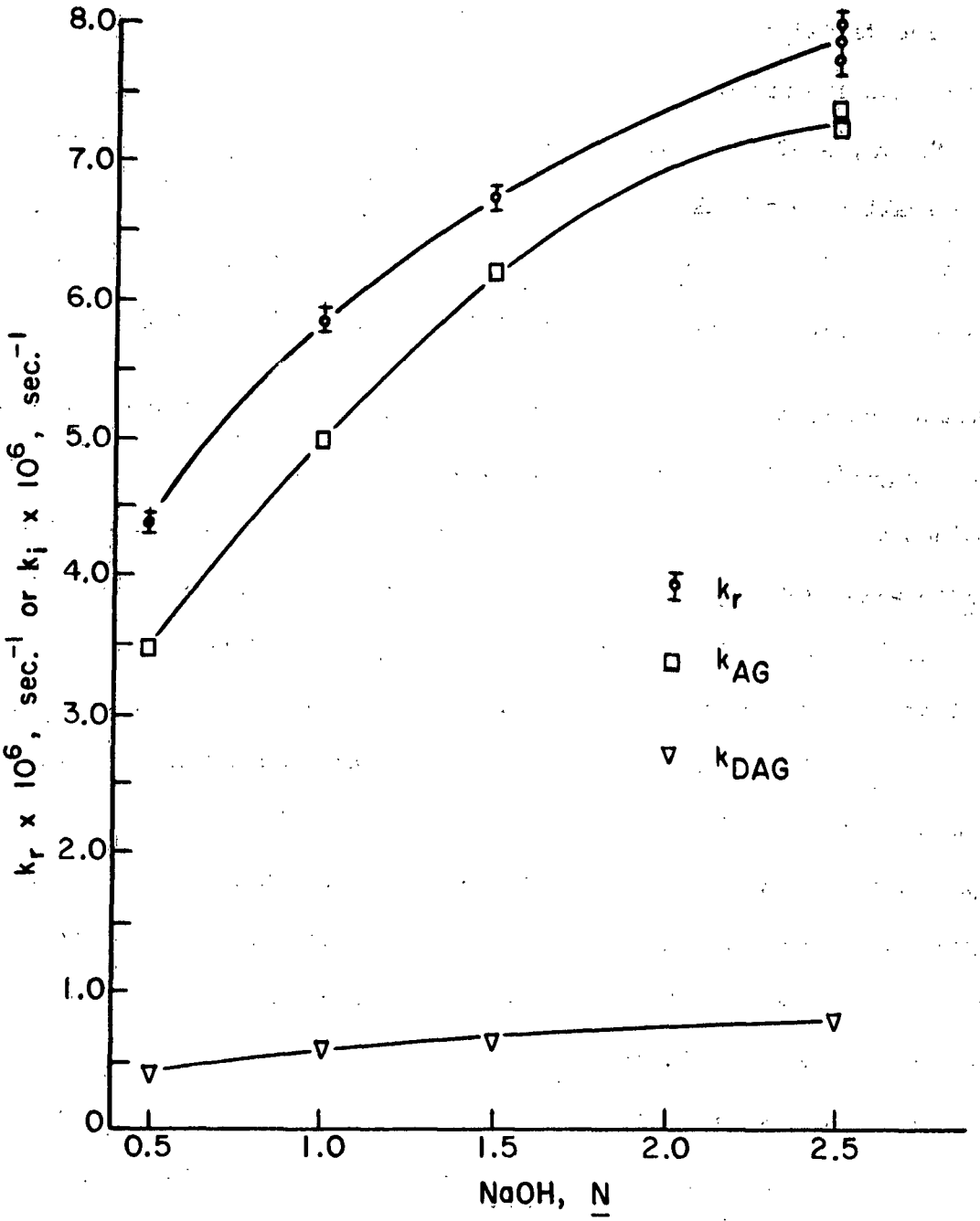


Figure 10. The Dependence of Pseudo-First-Order Rate Constants on Hydroxide Ion Concentration for the Alkaline Degradation of 1,5-Anhydrocellobiitol (0.1M) at 170°C.

The kinetic reaction order[6] with respect to hydroxide ion concentration, $\underline{b}$, calculated from the plot ln $\underline{k}$ vs. ln OH (Fig. 11) was not constant. The data points indicated in Fig. 11 are those which were determined experimentally for the alkaline degradation of 1,5-anhydrocellobiitol, while the smooth curve was generated with the aid of a linear, empirical correlation of $\underline{k}$ vs. ln [$^{-}$OH], (Fig. 12). The value of $\underline{b}$ calculated from the tangent to the curve generated by $\underline{k}_{\underline{r}}$ (the overall rate of alkaline degradation) (Fig. 11) was 0.29 at 2.5$\underline{N}$ NaOH and 0.53 at 0.5$\underline{N}$ NaOH. The value of $\underline{b}$ calculated similarly using $\underline{k}_{AG}$ (the rate of appearance of 1,5-anhydroglucitol) was 0.30 at 2.5$\underline{N}$ NaOH and 0.69 at 0.5$\underline{N}$ NaOH.

The product distribution was a function of the hydroxide ion concentration (Table II). Comparing the product distribution at 0.5$\underline{N}$ sodium hydroxide, 2.0$\underline{F}$ sodium $\underline{p}$-toluenesulfonate to that at 2.5$\underline{N}$ sodium hydroxide, the mole fraction of 1,5-anhydro-D-glucitol ($\underline{X}_{AG,\infty}$) produced increased about 15% and the mole fraction of 1,5:3,6-dianhydrogalactitol ($\underline{X}_{DAG,\infty}$) produced increased 10%. In addition, at the lower hydroxide ion concentration (0.5$\underline{N}$) the mole fractions of $\underline{X}_{AG,\infty}$ and $\underline{X}_{DAG,\infty}$ did not account for all the degradation products (Table II). The mole fraction of unaccounted for material, $\underline{X}_{UI,\infty}$, at 0.108 is comparable to $\underline{X}_{DAG,\infty}$. This material is thought to be either ionic in nature or small fragments of an original pyranose ring structure. In either event, the material would not be detectable by the GLC techniques used in the regular analysis procedure and will be referred to as the unidentified product(s). The mole fraction of unidentified product(s) decreased as the hydroxide ion concentration increased and appeared to become essentially zero at 1.5$\underline{N}$ sodium hydroxide (Table II). The hydroxide ion concentration at which the unidentified product(s) were essentially zero could not be established accurately, however, as the error in the mole

[6]From Equation (3) $\underline{k}_{\underline{r}} = \underline{k}[^{\ominus}OH]^{\underline{b}}$, hence, ln $\underline{k}_{\underline{r}}$ = ln $\underline{k}$ + $\underline{b}$ ln[$^{-}$OH].

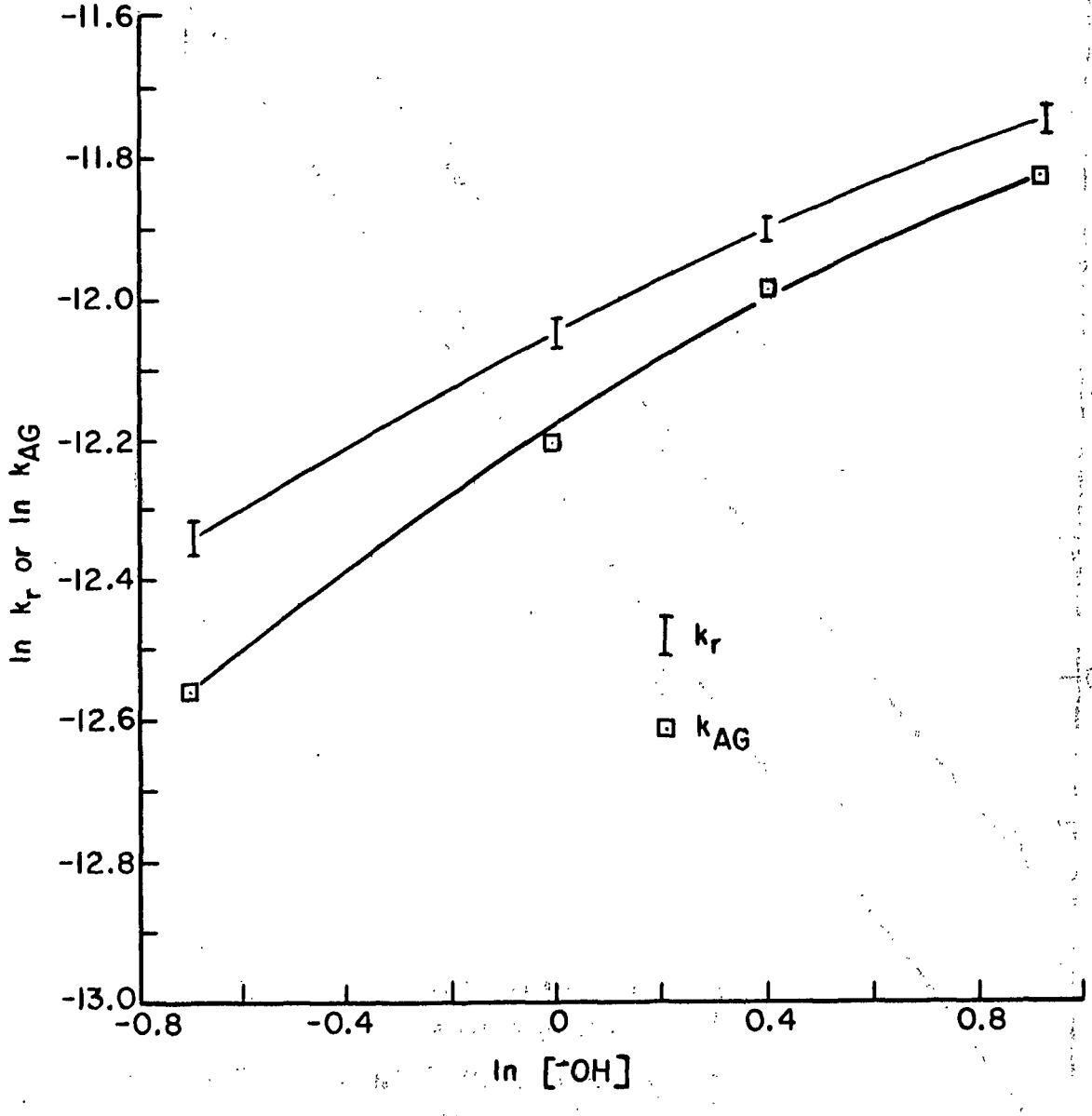


Figure 11. The Determination of the Empirical Reaction Order with Respect to the Hydroxide Ion Concentration for the Alkaline Degradation of 1,5-Anhydrocellobiitol (0.01M) at 170°C.

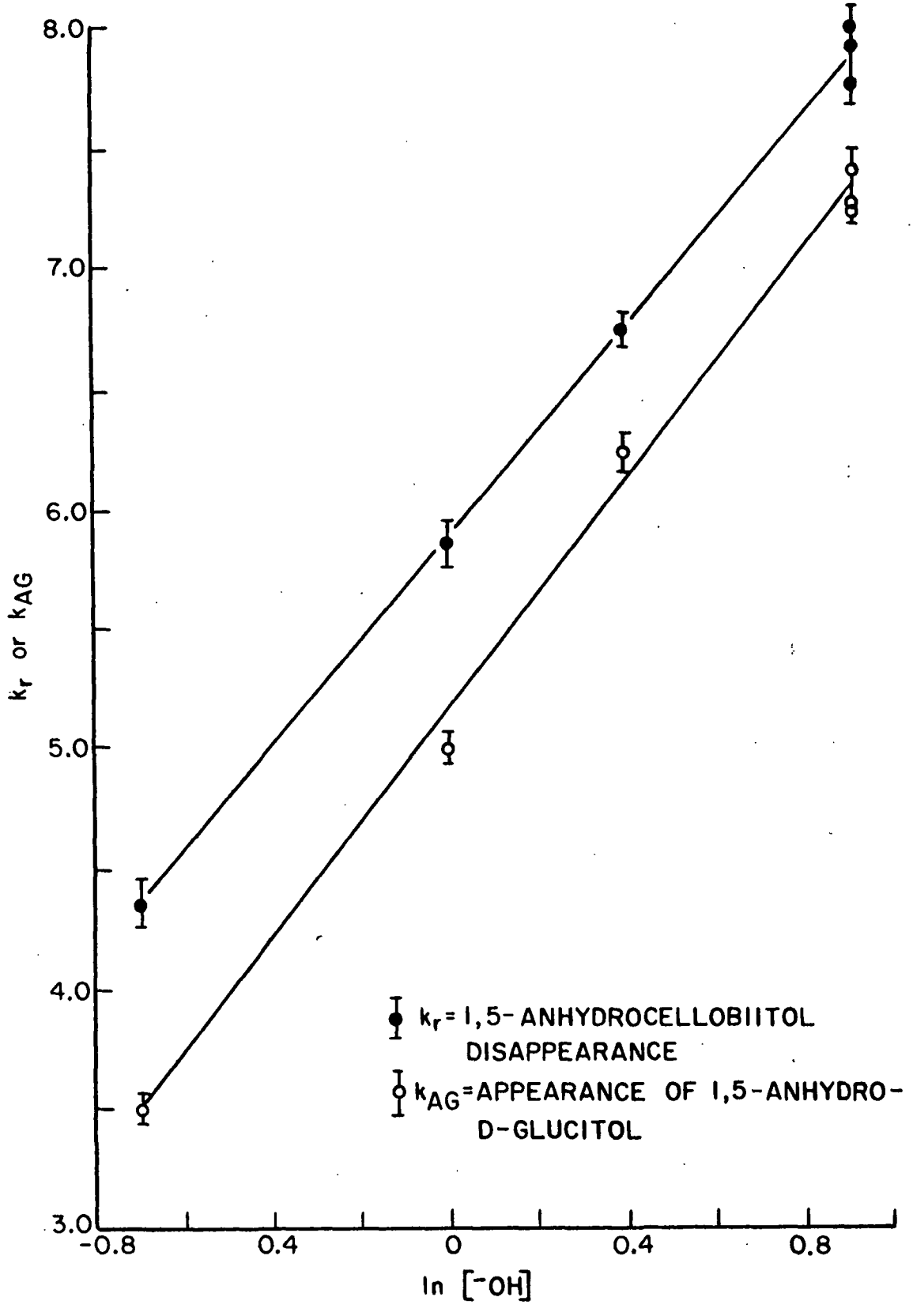


Figure 12. Linear Correlation Between the Pseudo-First-Order Rate Constant and Hydroxide Ion Concentration for the Alkaline Degradation of 1,5-Anhydrocellobiitol at 170°C.

fractions $X_{AG,\infty}$ and $X_{DAG,\infty}$ used to calculate $X_{UI,\infty}$ were of the same order of magnitude as the mole fraction of unidentified products, $X_{UI,\infty}$.

The small amount of 1,5-anhydro-D-gulitol found in the reaction mixture appeared to decrease slightly from a mole fraction of 0.007 to 0.005 as the hydroxide ion concentration increased from 0.5N to 2.5N. However, the accuracy of the determination is not sufficient to be certain the observed difference is real.

The mole fraction of 1,6-anhydro-β-D-glucopyranose, $X_{L,\infty}$, formed during the alkaline degradation of 1,5-anhydrocellobiitol (Table II) was only 0.26 at 0.5N NaOH and increased to about 0.33 at 2.5N NaOH.

EFFECT OF VARYING IONIC STRENGTH AT CONSTANT HYDROXIDE ION CONCENTRATIONS

The dependence of the pseudo-first-order constants for the alkaline degradation of 1,5-anhydrocellobiitol on ionic strength at constant hydroxide ion concentration was determined in 0.5 and 1.0N NaOH at 170°C. (Table III).

The pseudo-first-order rate constant (k_r) for 1,5-anhydrocellobiitol degradation decreased approximately 6.5% when the ionic strength was increased to 2.5F in both 0.5 and 1.0N NaOH (Table III). The effect of increasing ionic strength on product distribution varied for the two alkali levels. The mole fraction of 1,5-anhydro-D-glucitol formed ($X_{AG,\infty}$) decreased from 0.89 to 0.80 in 0.5N NaOH but only from 0.87 to 0.86 in 1.0N NaOH as the ionic strength was increased to 2.5F. The value of $X_{DAG,\infty}$ increased approximately 11% (0.08 to 0.09, Table III) in 0.5N NaOH but remained essentially constant (0.10) in 1.0N NaOH. The mole fraction of unidentified products ($X_{UI,\infty}$, Table III) thus increased about threefold at 0.5N NaOH, but only about 48% at 1.0N NaOH.

TABLE III

EFFECT OF VARYING IONIC STRENGTH AT CONSTANT HYDROXIDE ION CONCENTRATION ON THE ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) AT 170°C.

NaOH, N	NaTOS, F	$k_r \times 10^6$, $sec.^{-1}$	$X_{AG,\infty}$	$X_{DAG,\infty}$	$X_{UI,\infty}$ [a]	$X_{L,\infty}$ [b]
1.0	0.0	6.24 ± 0.08	0.873	0.096	0.031	0.31
1.0	1.5	5.84 ± 0.11	0.856	0.098	0.046	0.31
0.5	0.0	4.69 ± 0.08	0.887	0.083	0.030	0.30
0.5	2.0	4.38 ± 0.11	0.801	0.091	0.108	0.26

[a] See footnote d, Table II.

[b] See footnotes e and f, Table II.

EFFECT OF VARYING NUCLEOPHILE

The rate of alkaline degradation of 1,5-anhydrocellobiitol was essentially unaffected by the addition to the reaction system of an ion with a higher nucleophilicity than the hydroxide ion (Table IV). Sodium iodide was used instead of sodium p-toluenesulfonate to maintain constant ionic strength; thus, the effect of a more nucleophilic species than ^-OH could be determined. While the overall rate of degradation of 1,5-anhydrocellobiitol decreased about 10% in the presence of sodium iodide relative to that observed in the presence of sodium p-toluenesulfonate, the product distributions were almost identical.

TABLE IV

THE EFFECT OF THE PRESENCE OF SODIUM IODIDE ON THE ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) AT 170°C.

NaOH, N	NaTOS, F	NaI, F	$k_r \times 10^6$, sec.$^{-1}$	$X_{AG,\infty}$	$X_{DAG,\infty}$	$X_{UI,\infty}$
0.5	2.0	0.0	4.38 ± 0.11	0.801	0.091	0.108
0.5	0.0	2.0	3.94 ± 0.07	0.787	0.096	0.117

The value of $X_{L,\infty}$ was not determined rigorously as the rate of levoglucosan degradation (k_{dL}) in 0.5N NaOH, 2.0F NaI was not determined. However, if the value of k_{dL} determined in 0.5N NaOH, 2.0F NaTOS is applicable to the NaI system, then a value for k_{fL} can be calculated for the NaI system from Equation (15). The value of $X_{L,\infty}$ so obtained is comparable to that found in the presence of sodium p-toluenesulfonate. The applicability of the value for k_{dL} used in the above calculation is not certain, however, as the degradation mechanism for levoglucosan has not been established.

EFFECT OF TEMPERATURE

The Arrhenius activation energies (E_{expt}) were calculated by the method of least squares from the logarithmic form of the Arrhenius equation [Equation (17)]:

$$k = A \exp(-E_{expt}/RT) \tag{16}$$

or

$$\ln k = \ln A - E_{expt}/RT \tag{17}$$

where k = specific rate constant, sec.$^{-1}$,

A = "frequency factor" (empirical correlation coefficient), sec.$^{-1}$,

$\underline{R}$ = gas constant, 1.987 cal. deg.$^{-1}$ mole^{-1}, and

$\underline{T}$ = temperature, °K.

The enthalpy of activation ($\Delta\underline{H}^*$) was calculated from Equation (18) (27):

$$\Delta H^* = E_{expt} - RT + P\Delta V^* \qquad (18)$$

where $P\Delta\underline{V}^* \cong 0$, since $\Delta\underline{V}^*$, the volume change in the reaction, is virtually zero for dilute aqueous solutions.

The entropy of activation ($\Delta\underline{S}^*$) was calculated from Equation (20) which is derived from the Arrhenius equation [Equation (16)] and the relationship between the specific rate constant and the entropy of activation [Equation (19)]. Equation (19) was derived from the theory of absolute reaction rates (27) which relates the free energy of activation ($\Delta\underline{F}^*$) to the specific rate constant.

$$k = (ekT/h) \exp(-E_{expt}/RT) \exp(\Delta S^*/R) \qquad (19)$$

where $\underline{k}$ = specific rate constant, sec.$^{-1}$,

e = base for Napierian logarithms, 2.7183,

k = Boltzmann's constant, 1.380 x 10^{-6} erg. deg.$^{-1}$, and

$\underline{h}$ = Planck's constant, 6.25 x 10^{-27} erg sec.

Hence

$$\Delta S^* = R \ln (A/T) + R \ln (h/ek)$$

$$= 1.987 \ln (A/T) - 49.2. \qquad (20)$$

The free energy of activation was calculated from Equation (21):

$$\Delta F^* = \Delta H^* - T\Delta S^*. \qquad (21)$$

The pseudo-first-order rate constants for the degradation of 1,5-anhydrocellobiitol between 160 and 180°C. in both 2.5$\underline{N}$ sodium hydroxide and 0.5$\underline{N}$

sodium hydroxide, 2.0F sodium p-toluenesulfonate are reported in Table V. The Arrhenius plots of the data in Table V are shown in Fig. 13.

TABLE V

TEMPERATURE EFFECTS ON THE ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) AT TWO ALKALI LEVELS AT CONSTANT IONIC STRENGTH BETWEEN 160 AND 180°C.

Temp., °C.	NaOH, N	NaTOS, F	$k_r \times 10^6$, sec.$^{-1}$	$X_{AG,\infty}$	$X_{DAG,\infty}$	$X_{UI,\infty}$ [a]
180	2.5	0.0	21.37 ± 0.43	0.890	0.103	0.008
170[b]	2.5	0.0	7.89 ± 0.11	0.925	0.100	0.0
160	2.5	0.0	3.21 ± 0.04	0.885	0.081	0.034
180	0.5	2.0	11.64 ± 0.22	0.838	0.102	0.060
170	0.5	2.0	4.38 ± 0.11	0.801	0.091	0.108
160	0.5	2.0	1.59 ± 0.03	0.874	0.088	0.038

[a] See footnote d, Table II.

[b] Average of three runs.

The slope of the curves in Fig. 13 appear to be constant which indicates that no major change in the reaction mechanism(s) occurs over the temperature range investigated. The similarity of slopes between 2.5N NaOH and 0.5N NaOH, 2.0F NaTOS indicate that the Arrhenius activation energy is independent of hydroxide ion concentration.

The estimated thermodynamic functions of activation for the alkaline degradation of 1,5-anhydrocellobiitol in 2.5N sodium hydroxide and 0.5N sodium hydroxide, 2.0F sodium p-toluenesulfonate at 170°C. are given in Table VI. The differences between the thermodynamic functions for the two hydroxide ion concentrations are not large enough to be considered significant. The difference in ΔH^* between the appearance of 1,5-anhydro-D-glucitol and the

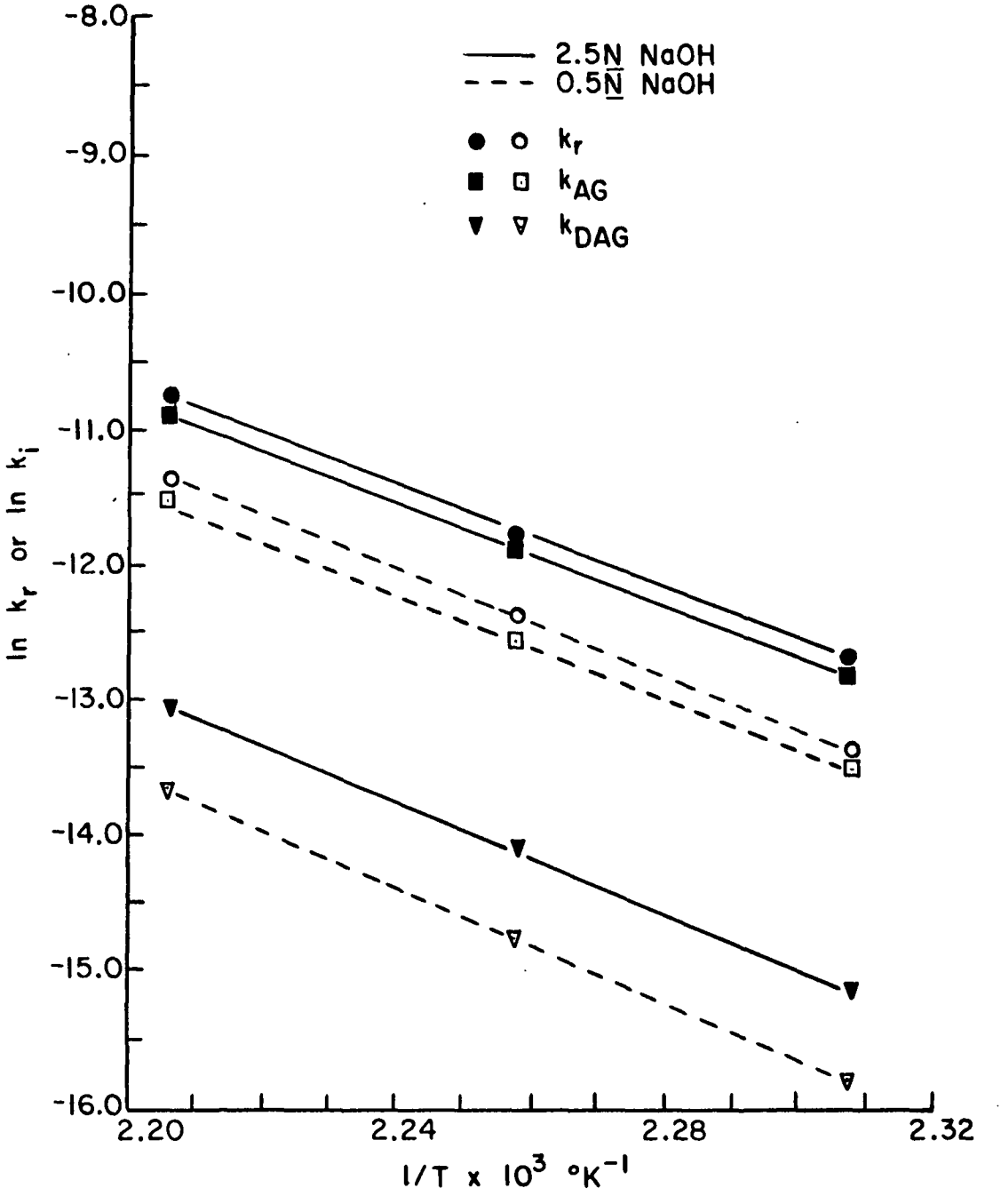


Figure 13. Arrhenius Correlations for the Alkaline Degradation of 1,5-Anhydrocellobiitol (0.01M) in 2.5N Sodium Hydroxide and 0.5N Sodium Hydroxide, 2.0F Sodium p-Toluenesulfonate Between 160 and 180°C.

appearance of 1,5:3,6-dianhydro-D-galactitol is considered significant. The difference between ΔS^* for these two compounds is probably large enough to be real but this is not certain.

TABLE VI

THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE ALKALINE DEGRADATION OF 1,5-ANHYDROCELLOBIITOL AT 170°C. FOR TWO ALKALI LEVELS AT CONSTANT IONIC STRENGTH (2.5F)

	Overall Degradation		Appearance AG		Appearance DAG	
	2.5N NaOH	0.5N NaOH	2.5N NaOH	0.5N NaOH	2.5N NaOH	0.5N NaOH
E_{expt}, kcal./mole	37.9	38.4	38.0	37.7	42.6	41.4
ΔH^*, kcal./mole	37.0	37.5	37.1	36.8	41.7	40.5
ΔS^*, cal./°K mole	+1.0	+0.9	+1.0	-1.1	+6.9	+2.9
ΔF^*, kcal./mole	36.6	37.1	36.7	37.3	38.6	39.2

Pseudo-first-order rate constants, used in the calculation of the thermodynamic functions, are dependent on hydroxide ion concentration. Thus, any errors introduced into the rate constants through variations in the hydroxide ion concentration due to temperature, would be reflected in the thermodynamic functions. At high hydroxide ion concentration the dependency of the rate of alkaline degradation of 1,5-anhydrocellobiitol on hydroxide ion concentration is small; thus, small changes in hydroxide ion concentration with temperature should have little effect on the rate constants determined. At low hydroxide ion concentration, however, the dependence of the rate constant on hydroxide ion is more significant, hence the hydroxide ion concentration was adjusted to compensate for the expansivity of water at the temperatures employed.

A second source of error involved the potential dependence of the pseudo-first-order rate constants on various ionic equilibrium constants. Any errors in the calculated activation functions due to temperature dependence of these equilibrium constants should be small since the temperature coefficients for ionic equilibria generally are small (28).

ALKALINE DEGRADATION OF 1,5-ANHYDROMALTITOL AT 170°C.

The pseudo-first-order rate constants for the alkaline degradation of 1,5-anhydromaltitol at 170°C. in varying ionic strength (1.5N NaOH, 1.0F NaTOS, and 1.5N NaOH) were determined (Table VII). Increasing the ionic strength to 2.5F at 1.5N NaOH increased the overall rate of reaction by about 7% and the rate of appearance of 1,5-anhydro-D-glucitol (k_{AG}) by about 4%.

TABLE VII

EFFECT OF VARYING IONIC STRENGTH ON THE ALKALINE DEGRADATION OF 1,5-ANHYDROMALTITOL (0.01M) AT 170°C.

NaOH, N	NaTOS, F	$k_r \times 10^6$, sec.$^{-1}$	$X_{AG,\infty}$	$X_{DAG,\infty}$	$X_{UI,\infty}$ [a]	$X_{L,\infty}$ [b]
1.5	1.0	1.16 ± 0.03	0.905	0.112	0.0	0.0
1.5	0.0	1.08 ± 0.03	0.935	0.130	0.0	0.0

[a] See footnote d, Table II.

[b] See footnotes e and f, Table II.

The overall rate constant, k_r, for the alkaline degradation of 1,5-anhydrocellobiitol (6.74×10^{-6} sec.$^{-1}$) was 5.8 times greater than k_r for 1,5-anhydromaltitol in 1.5N sodium hydroxide:1.0F sodium p-toluenesulfonate. The relative amounts of 1,5-anhydro-D-glucitol ($X_{AG,\infty}$) and 1,5:3,6-dianhydro-D-galactitol ($X_{DAG,\infty}$) formed was essentially the same for both systems (see

Tables II and VII). However, no 1,6-anhydro-β-D-glucopyranose (levoglucosan) was observed in the 1,5-anhydromaltitol reaction. Due to the low degradation rate of 1,5-anhydromaltitol a small amount of levoglucosan could, in theory, be formed but not detected. The point in the reaction when the maximum amount of levoglucosan would be present can be calculated by setting the derivative of Equation (15) with respect to time equal to zero [Equation (22)].

$$dL/dt = 0 = -L_o\, k_{dL} \exp(-k_{dL}t) - [k_{fL}R_o k_r/(k_{dL} - k_r)] \exp(-k_r t) + [k_{fL}R_o k_{dL}/(k_{dL} - k_r)] \exp(-k_{dL}t) \quad (22)$$

where $\underline{k_{fL}}$ = pseudo-first-order rate constant for formation of levoglucosan, $sec.^{-1}$,

$\underline{k_{dL}}$ = pseudo-first-order rate constant for degradation of levoglucosan, $sec.^{-1}$,

$\underline{k_r}$ = pseudo-first-order rate constant for disappearance of reactant, $sec.^{-1}$,

$\underline{R_o}$ = concentration of reactant at $\underline{t} = 0$, mole/liter,

$\underline{L_o}$ = concentration of levoglucosan, mole/liter at $\underline{t} = 0$, and

$\underline{t}$ = time, sec.

Rearrangement and simplification yields:

$$\exp[(k_{dL} - k_r)t] = k_{dL}/k_r - k_{dL}(k_{dL} - k_r)L_o/k_r k_{fL} R_o. \quad (23)$$

Taking the logarithm of Equation (23) gives Equation (24):

$$(k_{dL} - k_r)t = \ln [k_{dL}/k_r - k_{dL}(k_{dL} - k_r)L_o/k_r k_{fL} R_o]. \quad (24)$$

If $\underline{L_o} = 0$ then:

$$t_{max} = \ln(k_{dL}/k_r)/(k_{dL} - k_r) \quad \text{and} \quad (25)$$

evaluation of Equation (25) using $k_{dL} = 71 \times 10^{-6}$ sec.$^{-1}$ and $k_r = 1.16 \times 10^{-6}$ sec.$^{-1}$ yields $t_{max} = 5.88 \times 10^4$ sec.

Levoglucosan at a level of 2×10^{-5} mole/liter was routinely detected by the GLC analysis employed. If it is assumed that this amount of levoglucosan was actually present in the reaction mixture, then evaluation of Equation (15) using $L = 2 \times 10^{-5}$ mole/liter, $R_o = 1 \times 10^{-2}$ mole/liter of 1,5-anhydromaltitol, $L_o = 0$ and $t = 5.88 \times 10^4$ sec. would yield a value for k_{fL} of 1.5×10^{-7} sec.$^{-1}$ which corresponds to a value of 0.13 for the mole fraction of levoglucosan ($X_{L,\infty}$) formed during the alkaline degradation of 1,5-anhydromaltitol. The amount of levoglucosan which would be "just detectable" was not determined rigorously; however, it is probably less than 1×10^{-5} mole/liter. Since no levoglucosan could be detected in samples taken from the alkaline degradation of 1,5-anhydromaltitol near t_{max}, it is concluded that the mole fraction of levoglucosan ($X_{L,\infty}$) which could possibly be formed but not detected would feasibly be on the order of 0.05, but not exceeding 0.13.

ALKALINE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL AT 170°C.

The pseudo-first-order rate constants for the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol at 170°C. were determined at various hydroxide ion concentrations (0.5N-2.5N) at constant total ionic strength (2.5F), Table VIII. The overall rate constants increased with increasing hydroxide ion concentration in what appears to be a linear manner (Fig. 14), but a fivefold increase in the hydroxide ion concentration resulted in only a 2.9-fold increase in k. The reaction order with respect to hydroxide ion concentration as determined from the plot of ln k vs. ln [$^-$OH] (Fig. 15) was constant with a value of 0.63 based on k_r and 0.66 based on k_{AG}. This is

in sharp contrast to the kinetic order with respect to hydroxide ion concentration determined for the alkaline degradation of 1,5-anhydrocellobiitol which is strongly dependent upon the hydroxide ion concentration.

TABLE VIII

EFFECT OF VARYING HYDROXIDE ION CONCENTRATION AT CONSTANT IONIC STRENGTH ON THE ALKALINE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL AT 170°C.

NaOH, N	NaTOS, F	$k_r \times 10^6$, sec.$^{-1}$	$X_{TMAG,\infty}$	$X_{UI,\infty}$ [a]	$X_{L,\infty}$ [b]
2.5	0.0	8.49 ± 0.42	0.875	0.125	0.64
1.5	1.0	6.37 ± 0.32	0.761	0.239	0.65
0.5	2.0	3.10 ± 0.14	0.829	0.171	0.53

[a] See footnote d, Table II.

[b] See footnotes e and f, Table II.

The pseudo-first-order rate constants determined for the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol were of a lower precision (± 5%) than those determined for 1,5-anhydrocellobiitol (± 2%). The reasons for this are not well understood but are believed to be related to the GLC conditions required for the analysis of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (TMAG) and 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (TMAC).

As a result of the greater uncertainty in the rate constants, the mole fraction of unidentified product(s) (determined by difference between k_r and k_{TMAG}) was somewhat erratic. However, the product distribution appears similar to that observed with 1,5-anhydrocellobiitol. In making this comparison it must be remembered that the formation of 1,5:3,6-dianhydro-D-galactitol is not

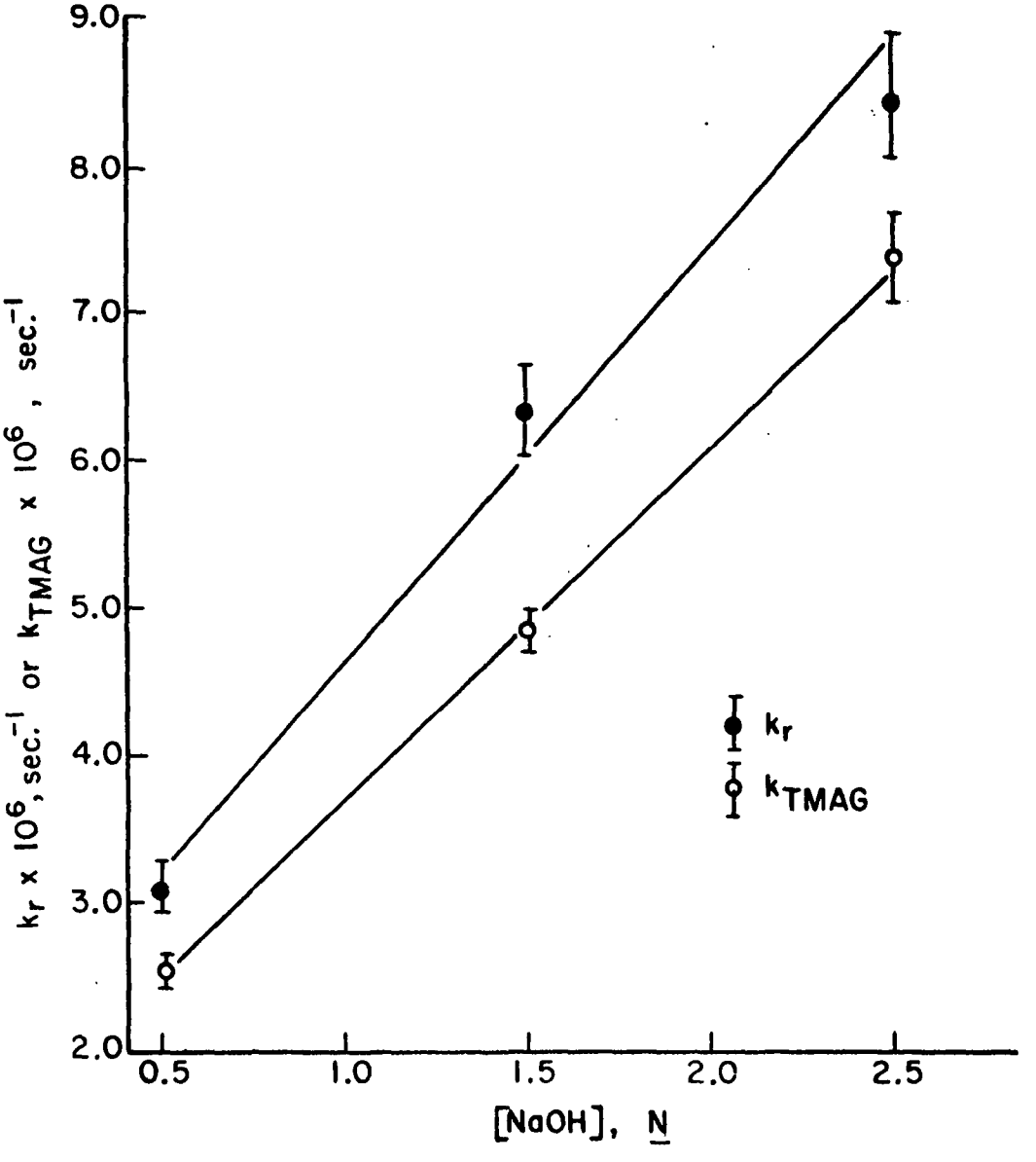


Figure 14. The Dependence of the Pseudo-First-Order Rate Constants on Hydroxide Ion Concentration for the Alkaline Degradation of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol (0.01M) at 170°C.

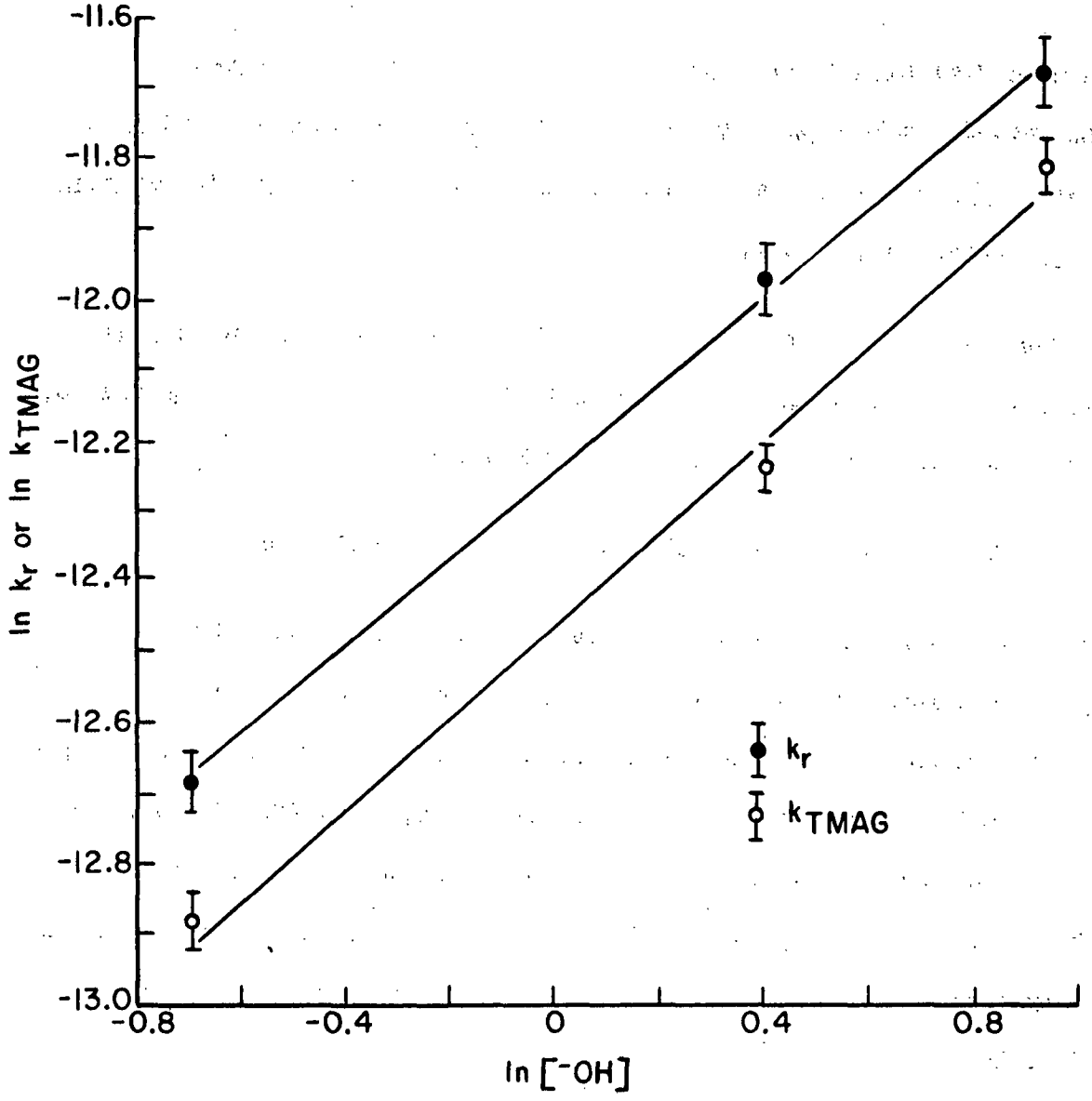


Figure 15. Determination of the Empirical Reaction Order with Respect to Hydroxide Ion Concentration for the Alkaline Degradation of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol at 170°C.

possible when 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol is the reactant; thus, the unidentified product(s) correspond to the sum of the 1,5:3,6-di-anhydro-D-galactitol and the unidentified product(s) observed in 1,5-anhydro-cellobiitol degradation.

The mole fraction of levoglucosan formed in the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol ranged from 0.53 at 0.5N NaOH to 0.64 at 2.5N NaOH and was about double that formed in the alkaline degradation of 1,5-anhydrocellobiitol.

The overall degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol at 2.5N NaOH was 8% faster than 1,5-anhydrocellobiitol; at 0.5N NaOH, the rate of degradation was 29% slower than 1,5-anhydrocellobiitol.

ALKALINE DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE

The pseudo-first-order rate constants for the alkaline degradation of 1,6-anhydro-β-D-glucopyranose (levoglucosan) were required to calculate the amount of levoglucosan formed in the alkaline degradation of the various disaccharide reactants. The rate constants were determined at 170°C. for varying hydroxide ion concentrations at constant ionic strength and varying ionic strength (Table IX). The specific rate constant for 2.5N sodium hydroxide was obtained by extrapolation of the linear empirical correlation of k_{dL} vs. ln $[^{\ominus}OH]$ (Fig. 16).

The rate of alkaline degradation of levoglucosan increased in a nonlinear manner as the hydroxide ion concentration increased; a fivefold increase in hydroxide ion concentration resulted in a 3.9-fold increase in the pseudo-first-order rate constant at a constant ionic strength.

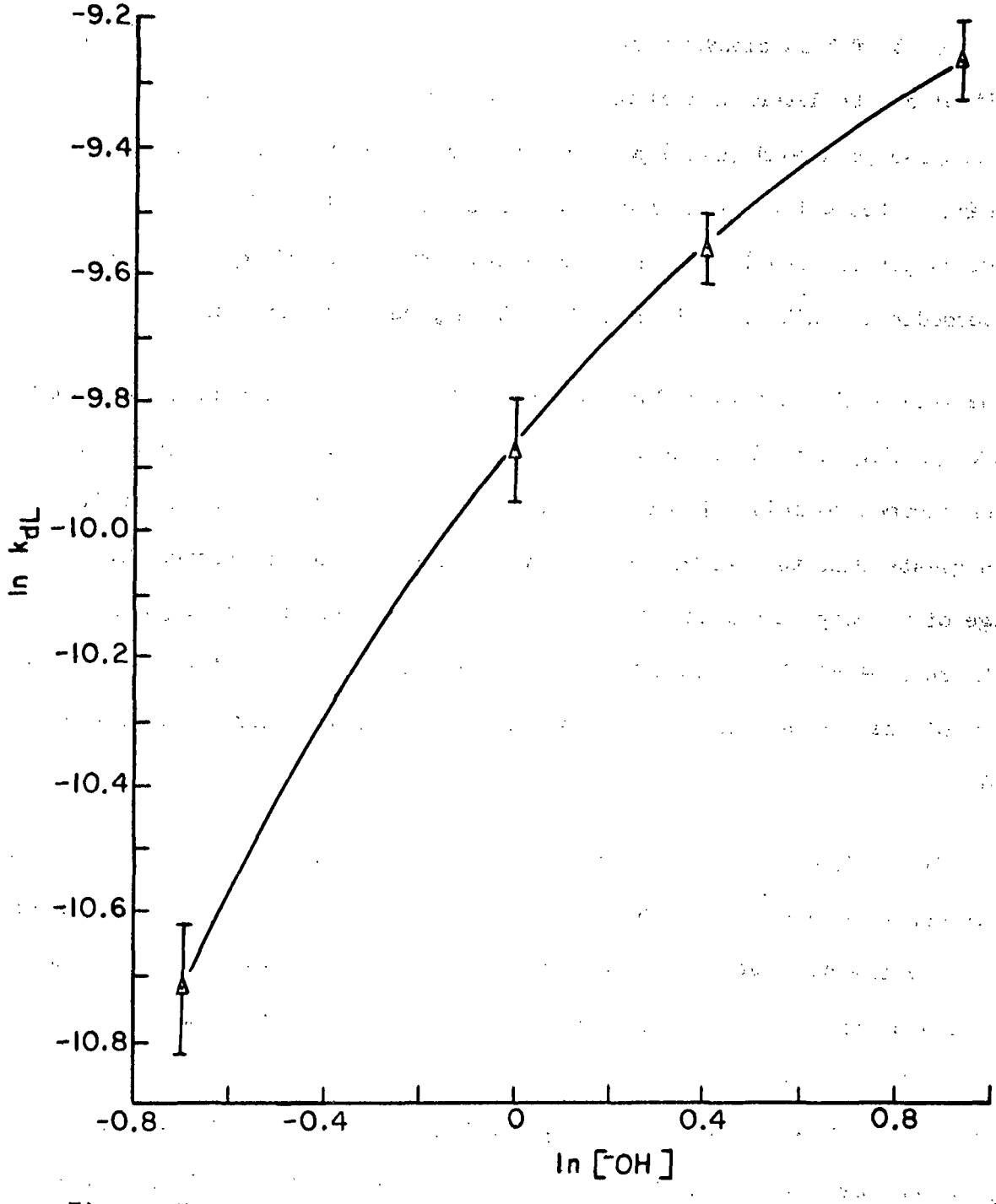


Figure 17. Determination of the Empirical Reaction Order with Respect to Hydroxide Ion Concentration for the Alkaline Degradation of 1,6-Anhydro-β-D-glucopyranose at Constant Ionic Strength at 170°C.

DISCUSSION OF RESULTS

POINT OF BOND CLEAVAGE

The point of bond cleavage in the alkaline degradation of 1,5-anhydrocellobiitol can be determined by product analysis (Fig. 18). Cleavage of the glucosyl-oxygen bond (a-a') produces 1,5-anhydro-D-glucitol (stable) (XX) and intermediates which result from the D-glucopyranosyl moiety. Cleavage of the oxygen-aglycon bond (b-b') produces a β-D-glucopyranosyloxy anion (IVa) and intermediates which result from the 1,5-anhydro-D-alditol moiety.

The intermediates formed from the D-glucopyranosyl moiety by cleavage of the glycosyl-oxygen bond can generate either 1,6-anhydro-β-D-glucopyranose (III) or degrade to acidic products. There is no evidence in the literature which suggests that the β-D-glucopyranosyloxy anion, which is formed from cleavage of the oxygen-aglycon bond, can form 1,6-anhydro-β-D-glucopyranose. 1,5-Anhydro-D-glucitol has been demonstrated to be stable to hot alkali; hence, cleavage of the oxygen-aglycon bond is the only route to other 1,5-anhydro-alditols.

The diagnostic tools for determining the point of bond cleavage from product analysis can be summarized as follows. Cleavage at the oxygen-aglycon bond is evidenced by the formation of 1,5-anhydro-D-alditol products other than 1,5-anhydro-D-glucitol, but is not precluded by the formation of 1,5-anhydro-D-glucitol. Cleavage at the glycosyl-oxygen bond is evidenced by the formation of 1,6-anhydro-β-D-glucopyranose but not precluded by the lack of 1,6-anhydro-β-D-glucopyranose production. Cleavage at the glycosyl-oxygen bond is strongly suggested when the major product of alkaline degradation is 1,5-anhydro-D-glucitol.

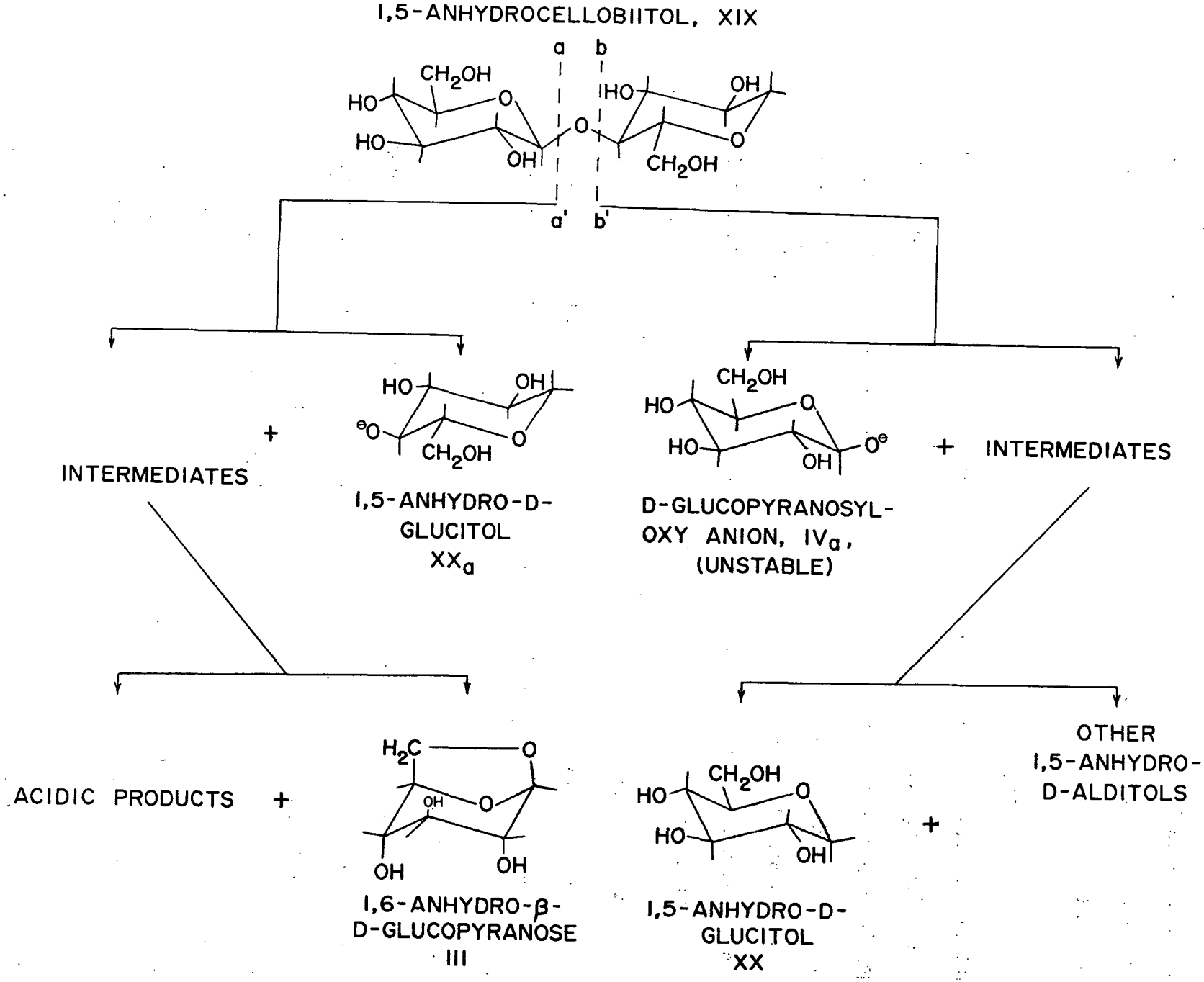


Figure 18. Schematic Representation of Possible Points of Bond Cleavage and Resulting Products

The major product in the alkaline degradation of 1,5-anhydrocellobiitol is 1,5-anhydro-D-glucitol (80-90%)[7]. 1,6-Anhydro-β-D-glucopyranose (31%)[7] is also formed during the degradation. Thus, degradation is occurring at the glycosyl-oxygen bond.

1,5-Anhydroalditols other than 1,5-anhydro-D-glucitol, which have been identified are 1,5:3,6-dianhydro-D-galactitol (XXI) (ca. 10%), 1,5-anhydro-D-gulitol (XXII) (ca. 0.5%), and 1,5-anhydro-D-galactitol (XXIII) (trace). An unidentified product(s) which constitutes 0-10% of the products, depending on degradation conditions, is also formed. Since cleavage of the glycosyl-oxygen bond forms stable 1,5-anhydro-D-glucitol, production of the unidentified product(s) must result from cleavage of the oxygen-aglycon bond. Thus, it is concluded that bond cleavage also occurs at the oxygen-aglycon bond.

It has been previously reported (20,23) that alkaline degradation of the glycosidic linkages can result in cleavage of both the glycosyl-oxygen bond and the oxygen-aglycon bond. Best (20) reported that in methyl β-cellobioside cleavage occurred 11% of the time at the oxygen-aglycon bond of the methyl-cellobiosyl linkage but that no evidence for cleavage of the oxygen-aglycon bond of the glucosyl-methyl glucoside linkage (analogous to glycosidic linkage in 1,5-anhydrocellobiitol) could be found. This can easily be rationalized, however, by noting that the major identified product from cleavage of the oxygen-aglycon bond in 1,5-anhydrocellobiitol (1,5:3,6-dianhydro-D-galactitol) locks the pyranose ring in the 1C conformation. The analogous compound in Best's system (20), methyl 3,6-anhydro-β-D-galactopyranoside, should therefore be locked in the required conformation for a M-C mechanism to be operative and

[7]Percentages are based on the total amount of 1,5-anhydrocellobiitol degraded.

alkaline degradation probably occurs quite rapidly. Thus, verification of oxygen-aglycon bond cleavage in the glucosyl-methyl glucoside linkage in methyl β-cellobioside would be difficult.

Robins (23) also reported that in the alkaline degradation of methyl α-D-glucopyranoside cleavage occurs 5% of the time at the oxygen-aglycon bond.

POSSIBLE MECHANISMS AND THEIR THEORETICAL CHARACTERISTICS

GENERAL

Historically only ionic mechanisms have been considered in the oxygen-free alkaline cleavage of glycosidic linkages (8,10,19,23). However, McCloskey (29) has postulated a free radical mechanism for the oxygen-alkali degradation of methyl β-D-glucopyranoside. A rigorous investigation of the possibility of radical mechanisms in the oxygen-free alkaline cleavage of the glycosidic linkages has not been made; however, the available evidence from both previous work and this study does not indicate that radical mechanisms are operative. In particular, the reactions do not exhibit induction periods, are base-catalyzed, and exhibit media dependencies typical of polar reactions. Thus, in the oxygen-free alkaline degradation of 1,5-anhydrocellobiitol the following three ionic mechanisms will be considered: bimolecular nucleophilic substitutions (S_N2), unimolecular nucleophilic displacement by the conjugate base of a neighboring group (S_N1cB), and unimolecular nucleophilic substitution (S_N1).

The distinguishing theoretical characteristics of S_N1, S_N1cB, and S_N2 mechanisms are based on experimental work done at or near room temperature. Very little is known about how these theoretical characteristics apply to similar reactions in nonideal solutions at high temperature, i.e., 170°C.

In particular, the effect of elevated temperatures on the activity coefficients and equilibrium constants for the carbohydrates and aqueous alkali are unknown. In addition, reference data for nucleophilic substitution reactions at elevated temperatures are very limited. With the above limitations in mind, it will be assumed that the theoretical characteristics advanced for the various reaction mechanisms at room temperature are applicable at least in order and direction at 170°C.

BIMOLECULAR NUCLEOPHILIC SUBSTITUTION (S_N2)[8]

The S_N2 mechanism is a one-step reaction in which one nucleophile displaces another. The transition state [Equation (26)] is both the rate-controlling and product-controlling step for the reaction

$$\underset{\text{Attacking Nucleophile}}{X^-} + \underset{\text{Reactant}}{R\text{-}Y} \longrightarrow \underset{\text{Transition State}}{X^{\delta-}\text{--}R\text{--}Y^{\delta-}} \longrightarrow \underset{\text{Products}}{X\text{-}R + Y^-} . \qquad (26)$$

The attacking nucleophile begins to form the "new" covalent bond simultaneously with the initiation of cleavage of the "old" covalent bond. Thus, the reaction proceeds with inversion of configuration at the reaction site. Inversion of configuration is readily discernible when the reaction site is an asymmetric carbon atom and the product is isolable.

The reaction is first-order with respect to both the reactant and the attacking nucleophile and its rate is directly related to the nucleophilicity of the attacking nucleophile. When the attacking nucleophile is negatively

[8]For a more thorough discussion of nucleophilic substitution reactions see Hine (14), Streitwieser (24), or Gould (30).

charged, the rate constant is inversely dependent on the total ionic strength of the reaction system since the dispersal of charge in the transition state is hindered by increasing ionic strength.

UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION BY THE CONJUGATE BASE OF A NEIGHBORING GROUP (S_N1cB)

The S_N1cB mechanism is essentially an S_N2 mechanism with the exception that the attacking nucleophile is now some functional group attached to the reactant molecule; thus, the rate-determining step is unimolecular. Because of the close proximity of the neighboring group and, hence, its availability for reaction, S_N1cB mechanisms are generally much faster than a similar S_N2 mechanism.

UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION (S_N1)

The S_N1 mechanism consists of an initial heterolysis to form a carbonium ion which subsequently reacts to form more stable products [Equations (27)-(29)].

$$\underset{\text{Reactant}}{R\text{-}Y} \longrightarrow \underset{\text{Transition State}}{R^{\delta+}\cdots Y^{\delta-}} \longrightarrow \underset{\text{Carbonium Ion}}{R^+} + \underset{\text{Leaving Group}}{Y^-} \qquad (27)$$

$$\underset{\text{Carbonium Ion}}{R^+} + \underset{\text{Nucleophile}}{X^-} \longrightarrow \underset{\text{Product}}{R\text{-}X} \qquad (28)$$

$$\underset{\text{Carbonium Ion}}{R^+} \longrightarrow \underset{\text{Transition State, elimination of hydrogen}}{R^{\delta+}\cdots H^{\delta+}} \longrightarrow \underset{\text{Elimination Products}}{H^+ + R'} \qquad (29)$$

The heterolysis to form the carbonium ion is the rate-determining step in an S_N1 mechanism. Thus, the nucleophilicity of X^- has no effect on the rate. However, the nucleophilicity of X^- plus steric factors will determine the ratio of

direct nucleophilic substitution on the cationic site [Equation (28)] to proton elimination [Equation (29)]. The original carbonium ion may also rearrange to a more stable carbonium ion which then reacts further [e.g., Equations (28) and (29)]. Thus, there is the potential for a number of products when the reaction is governed by an S_N1 mechanism.

The reaction is first-order with respect to reactant and directly related to the total ionic strength since the separation of unlike charges in the transition state is enhanced by increasing ionic strength.

The substitution product of an S_N1 reaction mechanism may or may not be sterically inverted depending on steric factors and the degree of association between the carbonium ion and the leaving group.

THERMODYNAMIC DISTINCTIONS BETWEEN THE S_N2, S_N1cB, AND S_N1 MECHANISMS

The enthalpy of activation (ΔH^+) should be lower for an S_N2 or S_N1cB mechanism than an S_N1 mechanism for the same reaction (30). In the transition state of either an S_N2 or S_N1cB mechanism [Equation (26)] the "new" bond is forming while the "old" bond is being cleaved; hence, this conservation of energy lowers the required activation energy. In an S_N1 mechanism [Equation (27)] the "old" bond is essentially cleaved in the transition state and "new" bond formation proceeds from the primary kinetic product, the carbonium ion. Hence, the energy liberated from bond formation is unavailable to lower the activation enthalpy required in the transition state of the S_N1 mechanism. Brown and Hudson (31) report, in mechanistic studies of the hydrolysis of substituted benzoyl chlorides, that activation energies for S_N1 reactions were larger than those for S_N2 reactions, the difference between the two mechanisms being on the order of 8 kcal./mole.

The entropy of activation also reflects differences in the transition states of the S_N2-type mechanisms and the S_N1 mechanism. The partially bonded nature of the transition state of the S_N2 and S_N1cB mechanisms produces a loss of rotational, vibrational, and translational (S_N2 only) degrees of freedom (the system becomes more ordered). In the transition state of an S_N1 mechanism, an additional species is being created; thus, the degrees of freedom are being increased (less ordered system). Taking the entropy of activation for the S_N2 mechanism as a base point, ΔS^* for the S_N1cB mechanism will be more positive and ΔS^* for an S_N1 mechanism will be significantly more positive than ΔS^* for the S_N2 mechanism.

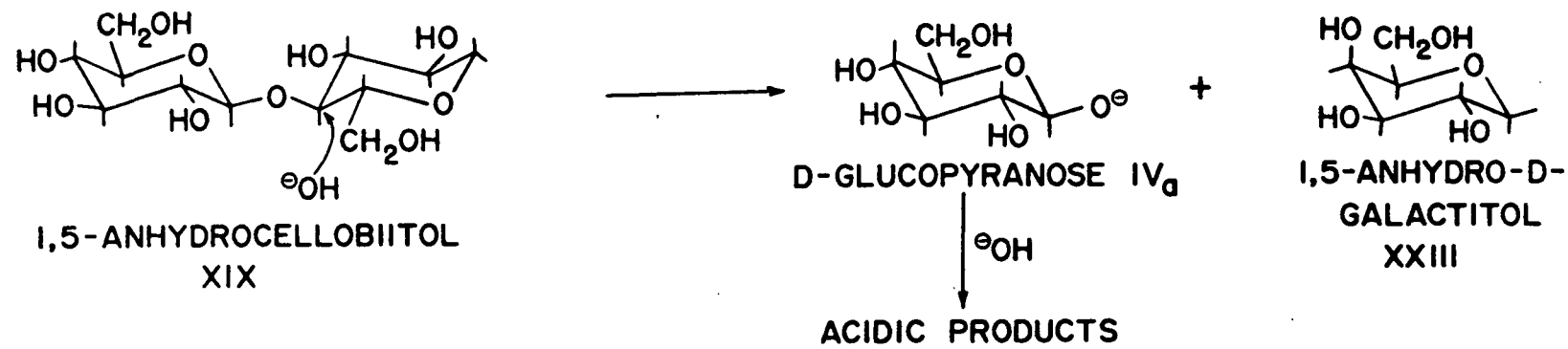
The difference in ΔS^* for A-1 and A-2 mechanisms (ester hydrolysis) may be as high as 30 e.u. (32). However, the spread for "typical" S_N1 and S_N2 mechanisms are generally not as large. Prediction or interpretation of the differences in the entropy of activation for a series of reaction mechanisms must be tempered with caution as the entropy of activation also reflects the environment (i.e., solvent) (32).

ELIMINATION OF THE S_N2 MECHANISM

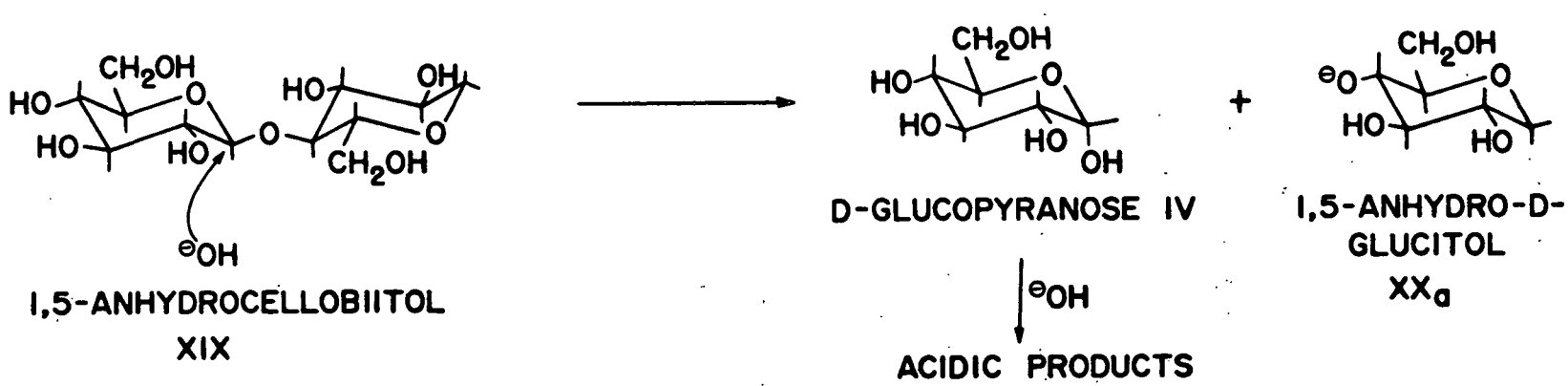
Cleavage of the oxygen-aglycon bond of 1,5-anhydrocellobiitol by an S_N2 mechanism (Fig. 19A) would involve nucleophilic attack by hydroxide ion at C-4 resulting in the production of 1,5-anhydro-D-galactitol (XXIII). Since only a trace of 1,5-anhydro-D-galactitol was observed in the reaction mixture, an S_N2 mechanism is not a viable route for cleavage of the oxygen-aglycon bond.

Unfortunately, product analysis is not diagnostic (except in special instances) for an S_N2 mechanism of glycosyl-oxygen bond cleavage[9] in 1,5-

[9]Cleavage of the glycosyl-oxygen bond results in the formation of 1,5-anhydro-D-glucitol irregardless of the mechanism involved.



A



B

Figure 19. Possible S_N2 Mechanisms for the Alkaline Degradation of 1,5-Anhydrocellobiitol; A) Oxygen-Aglycon Bond Cleavage, B) Glycosyl-Oxygen Bond Cleavage

anhydrocellobiitol (Fig. 19B). A more general method for detecting an S_N2 mechanism involves the inclusion in the reaction mixture of a more nucleophilic species than was formerly present. This procedure results in a marked increase in the reaction rate if the reaction is governed by an S_N2 mechanism but has essentially no effect on reactions governed by S_N1 or S_N1cB mechanisms. The observed effect on the alkaline degradation of 1,5-anhydrocellobiitol of introducing iodide ion (stronger nucleophile than hydroxide ion) into the reaction system while maintaining the ionic strength and hydroxide ion concentration constant was a 10% decrease in the overall degradation rate. Since this effect is opposite to what would be expected if an S_N2 mechanism were governing the degradation, it is apparent that the degradation route in 1,5-anhydrocellobiitol does not involve an S_N2 mechanism.

CLEAVAGE OF THE OXYGEN-AGLYCON BOND

Alkaline cleavage of the oxygen-aglycon bond is characterized primarily by the formation of 1,5:3,6-dianhydro-D-galactitol and the unidentified product(s). The experimental data will be discussed in light of potential mechanistic pathways for the formation of the above products.

POSSIBLE MECHANISMS

Potential $S_N1cB(3)$ Mechanism

Since the potential $S_N1cB(3)$ mechanism involves oxirane (epoxide) ring formation, a short digression on aldose oxiranes may be in order at this point[10]. Formation of the oxirane ring requires the attacking nucleophile

[10]For a more detailed discussion of oxiranes see Williams (33), Newth (34), and Parker and Isaacs (35).

(i.e., the vicinal alkoxy anion) be trans to the leaving group. In addition, a conformation must be available where the two groups can approach an antiperiplanar orientation (i.e., trans-diaxial). If a vicinal, trans-hydroxyl group is present after oxirane ring formation, the oxirane ring will migrate [e.g., migration in methyl 3,4-anhydro-α-D-galactopyranoside to form methyl 2,3-anhydro-α-D-gulopyranoside (36)] with the equilibrium ratio being determined by the relative stabilities of the two oxirane rings (33).

Oxirane derivatives of aldoses normally are cleaved to give a trans-diaxial, α-hydroxy product [Furst-Plattner rule (37)]. Apparent diequatorial oxirane ring opening (abnormal) are generally thought to be the result of trans-diaxial opening from a less stable or unfavored conformation. The product can then rapidly revert to the more stable form in which the two functional groups are equatorial (33). The literature does not suggest that oxirane ring opening ever takes place with carbon-carbon bond scission.

The $S_N1cB(3)$ mechanism, Fig. 20, for the alkaline degradation of the oxygen-aglycon bond in 1,5-anhydrocellobiitol (XIX) is envisioned as occurring with anchimeric assistance from the C-3 alkoxy anion (XIXa), which is trans to the leaving group (β-D-glucopyranosyloxy anion, IVa), to form 1,5:3,4-dianhydro-D-galactitol (XXIV). In order to achieve the requisite trans-diaxial conformation between the C-3 alkoxy anion and the aglycon (IVa), the pyranose ring must be in the 1C conformation. Migration of the 3,4-epoxide (XXIV) to the 2,3-epoxide (XXV) followed by the nucleophilic attack of the C-6 alkoxy anion at C-3 to yield 1,5:3,6-dianhydro-D-galactitol (XXI) (all in 1C conformation) should occur rapidly. Buchanan and Fletcher (36) have shown that methyl 3,4-anhydro-α-D-galactopyranoside is degraded in 1 hr. in refluxing 0.1N sodium hydroxide to

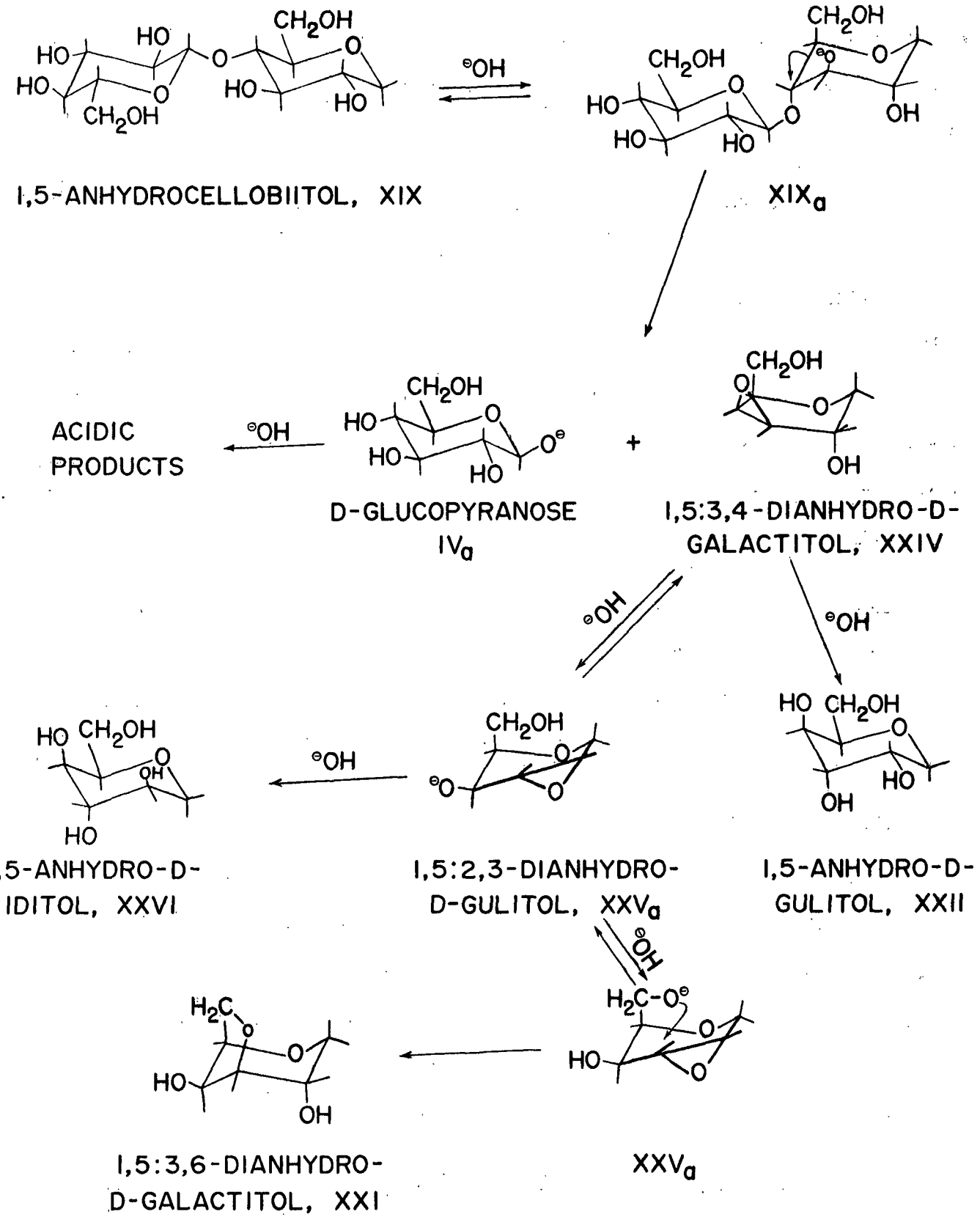


Figure 20. Potential $S_N1cB(3)$ Mechanism for the Alkaline Cleavage of the Oxygen-Aglycon Bond of 1,5-Anhydrocellobiitol

methyl 3,6-anhydro-α-D-galactopyranoside (crystalline yield, 71%). In addition, traces of methyl α-D-glucopyranoside and methyl α-D-idopyranoside were identified in the reaction mixture.

The C1 conformation is probably preferred in the 3,4- and 2,3-oxiranes, XXIV and XXV [based on parent aldoses (13) and, hence, oxirane ring cleavage by hydroxide ion should yield 1,5-anhydro-D-gulitol (XXII) and 1,5-anhydro-D-iditol (XXVI), respectively, which would be consistent with Buchanan's findings with methyl 3,4-anhydro-α-D-galactopyranoside (36). Oxirane ring cleavage by hydroxide ion of the 3,4- and 2,3-oxiranes, XXIV and XXV, from the 1C conformation would yield 1,5-anhydro-D-glucitol and 1,5-anhydro-D-galactitol, respectively.

Since all the products which can be formed from the initial 3,4-oxirane ring are expected to be stable based on the stability of 1,5-anhydro-D-glucitol, the $S_N1cB(3)$ mechanism cannot account for the production of the unidentified products.

Potential S_N1 Mechanism

If the alkaline cleavage of the oxygen-aglycon bond proceeds by a S_N1 mechanism (Fig. 21) the primary heterolysis products would be the glucopyranosyloxy anion (IVa) and the 1,5-anhydro-4-deoxy-D-xylo-hexitol-4-cation (XXVII). The glucopyranosyloxy anion will degrade very rapidly [half-life ca. 0.1 minute, (38)] to acidic products at 170°C. and 2.5N sodium hydroxide. The 1,5-anhydro-4-deoxy-D-xylo-hexitol-4-cation can feasibly react by a number of pathways.

The C-4 carbonium ion (XXVII) can react with hydroxide ion to yield a mixture of 1,5-anhydro-D-glucitol (XX) and 1,5-anhydro-D-galactitol (XXII). However, production of 1,5-anhydro-D-galactitol could potentially predominate if shielding of the carbonium ion by the leaving group is important.

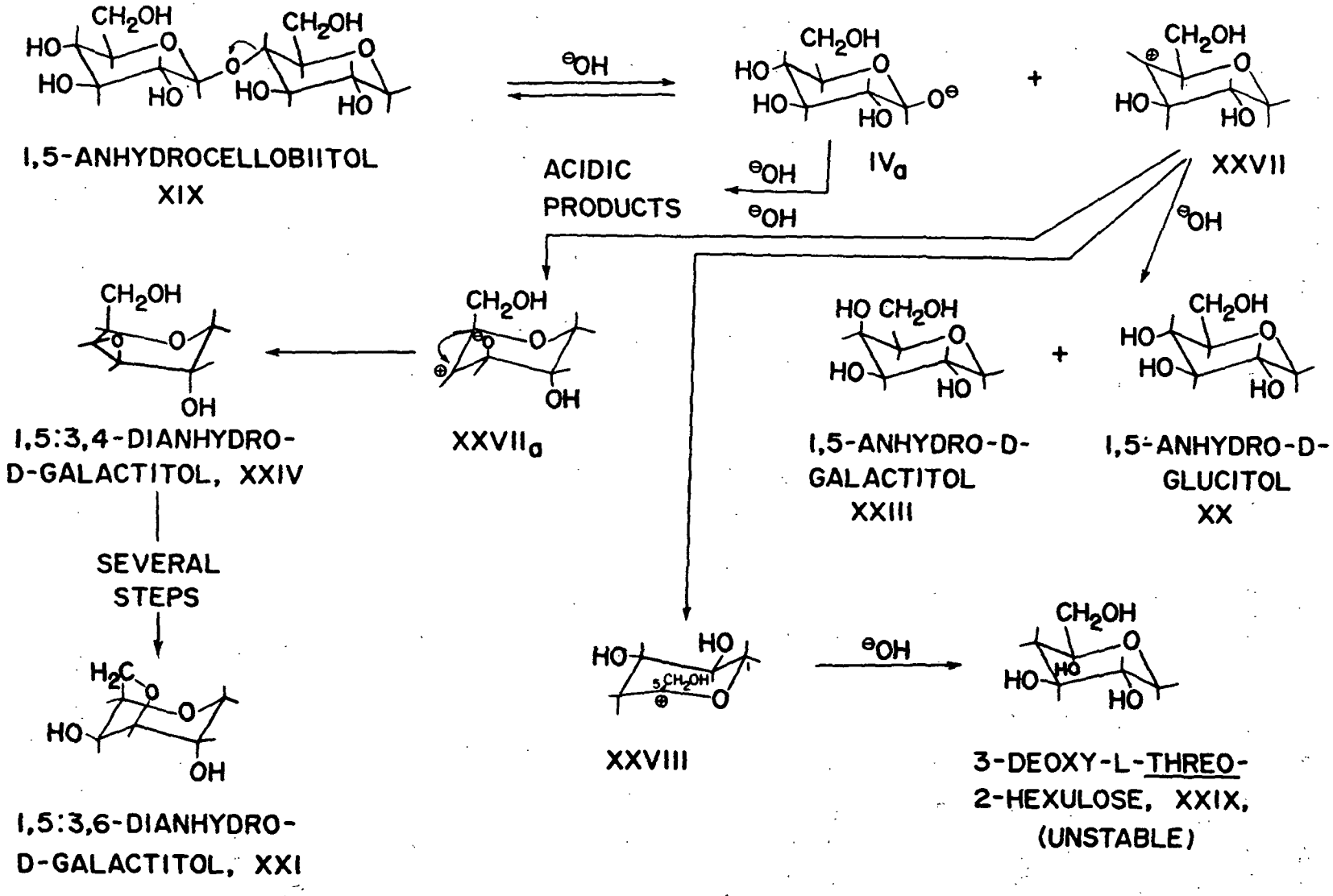


Figure 21. Potential S_N1 Mechanism for Alkaline Cleavage of the Oxygen-Aglycon Bond in 1,5-Anhydrocellobiitol

The C-4 carbonium ion (XXVII) could also undergo intramolecular nucleophilic attack by the C-3 hydroxyl or its oxy anion to yield 1,5:3,4-dianhydro-D-galactitol (XXI) for which further reaction paths have already been discussed (Fig. 20).

There are several potential reaction pathways for the C-4 carbonium ion which could lead to alkali-labile intermediate products and, hence, to the unidentified products.

Rearrangements of carbonium ions followed by nucleophilic substitution are well known (39). Rearrangement of the C-4 carbonium ion (XXVII) to a more stable C-5 carbonium ion (XXVIII) (resonance stabilized by pyranose ring oxygen) followed by reaction with hydroxide ion would yield 3-deoxy-L-threo-2-hexulose (XXIX). The C-4 carbonium ion (XXVII) could also rearrange to a C-3 carbonium ion (XXX) (Fig. 22) which would rapidly form 1,5-anhydro-4-deoxy-D-erythro-3-hexulose (XXXI). Alternately, the formation of XXXI could result from a concerted reaction in which proton transfer from C-3 to C-4 is concurrent with proton elimination from the C-3 hydroxyl. These compounds would be expected to degrade rapidly in hot alkali (40) and hence would be undetectable by the analytical methods employed.

Proton eliminations resulting in olefin formation are also frequently observed with carbonium ions (39). Elimination of a proton from C-3 of XXVII would result in the formation of a 3-4 enol (XXXII) which will be equilibrated with both 1,5-anhydro-4-deoxy-D-erythro-3-hexulose (XXI) and 1,5-anhydro-4-deoxy-D-threo-2-hexulose (XXXIII). Elimination of the C-5 proton would yield a 4-5 unsaturated sugar (XXXIV). Rearrangement to the C-5 carbonium ion (XXVIII) prior to elimination could also yield a 5-6 enol (XXXV). Since the stability of the unsaturated sugars (XXXIV and XXXV) is not known, the potential exists for these compounds to give rise to the unidentified products.

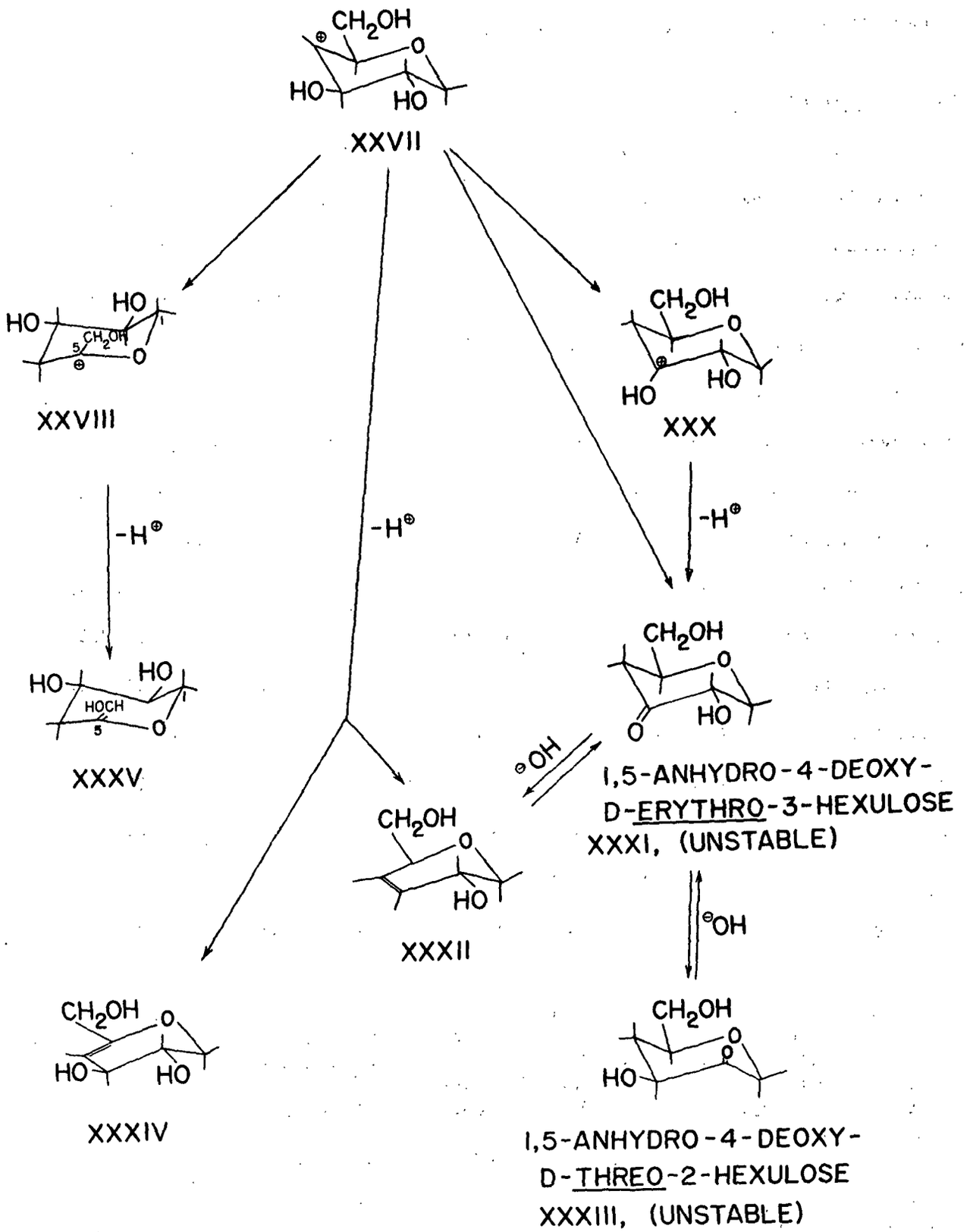


Figure 22. Potential Rearrangements of the 1,5-Anhydro-4-deoxy-D-xylo-hexitol-4-cation

COMPARISON OF OBSERVED DATA WITH POTENTIAL MECHANISMS

Product Analysis

Characterization of oxygen-aglycon bond cleavage would be greatly complicated if a significant amount of 1,5-anhydro-D-glucitol was formed during the process. If an S_N1 mechanism (Fig. 21) governed oxygen-aglycon cleavage, formation of 1,5-anhydro-D-glucitol would be accompanied by at least a comparable amount of 1,5-anhydro-D-galactitol formation if it resulted by reaction of hydroxide ion with the initial C-4 carbonium ion. Since essentially no 1,5-anhydro-D-galactitol was observed in the reaction mixture, 1,5-anhydro-D-glucitol is not formed as a direct result of C-4 carbonium ion formation. 1,5-Anhydro-D-glucitol could also potentially be formed by hydrolysis, in the 1C conformation, of the 3,4-oxirane ring of 1,5:3,4-dianhydro-D-galactitol (XXIV) formed in either an $S_N1cB(3)$ or S_N1 mechanism (Fig. 20 and 21). It is felt that very little (<1%) 1,5-anhydro-D-glucitol would be formed by this route principally because of Best's (20) observation that no ^{18}O was detected in the methyl β-D-glucopyranoside formed during cleavage of the associated (G-G) glycosidic linkage of methyl β-cellobioside[11] and Buchanan's observation that only D-gulose and D-idose derivatives were formed from methyl 3,4-anhydro-α-D-galactopyranoside (36). Thus, there is no reason to believe that oxygen-aglycon

[11]The methyl β-D-glucopyranoside formed from methyl β-cellobioside is comparable to the 1,5-anhydro-D-glucitol formed from 1,5-anhydrocellobiitol. The alditol or pyranoside initially formed by oxygen-aglycon bond cleavage must add an ^{-}OH from the solvent to form the "stable" product. If the alkali used is enriched with ^{18}O, incorporation of ^{18}O in the carbohydrate will take place and can be determined by mass spectrometry.

It should be noted that an ^{18}O incorporation study was not attempted with 1,5-anhydro-D-glucitol as no molecular ion can be found with acetate derivatives (loss of acetylium ion) and the TMS derivatives have a large M + 2 peak present normally (on the order of 25% of M) so detection of small changes associated with ^{18}O incorporation are not feasible. Use of the per-methylated derivatives was not attempted but may be feasible if a quantitative methylation can be carried out.

bond cleavage occurring by either an $S_N1cB(3)$ or an S_N1 mechanism should result in 1,5-anhydro-D-glucitol production.

The observed products of oxygen-aglycon bond cleavage, 1,5:3,6-dianhydro-D-galactitol (XXI) and 1,5-anhydro-D-gulitol (XXII), could be formed by either an $S_N1cB(3)$ or an S_N1 mechanism. 1,5-Anhydro-D-iditol, which could also be formed by either mechanism, could not be confirmed as a reaction product because a suitable standard was not available. However, there was an unidentified compound present in the reaction mixture which appeared in the GLC chromatogram in the region associated with known 1,5-anhydro-D-alditols. The concentration of this unidentified compound in the reaction mixture was comparable to that of 1,5-anhydro-D-gulitol ($X_{i,\infty}$ ca. 0.005).

The formation of the unidentified product(s) is consistent with only an S_N1 mechanism for oxygen-aglycon bond cleavage as all the potential products associated with the $S_N1cB(3)$ mechanism are stable. Alkaline cleavage of the oxygen-aglycon bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (XXXVI), which precludes an $S_N1cB(3)$ mechanism, results in the exclusive formation of unidentified product(s) (i.e., S_N1 mechanism). The fact that amounts of oxygen-aglycon bond cleavage in 1,5-anhydrocellobiitol (XIX) and its tri-O-methyl derivative (XXXVI) are comparable at the same conditions strongly suggests that oxygen-aglycon bond cleavage in the parent compound, 1,5-anhydrocellobiitol, occurs solely by an S_N1 mechanism.

The production of unidentified products in tri-O-methyl-1,5-anhydrocellobiitol allows speculation on which of the potentially alkali-sensitive compounds possible in an S_N1 mechanism (Fig. 21) are the most likely. It would appear that carbonium ion rearrangement to yield 3-deoxy-1,4,5-tri-O-methyl-L-threo-2-hexulose (methyl derivative of XXIX) or 1,5-anhydro-4-deoxy-2,6-di-O-methyl-D-

erythro-3-hexulose (methyl derivative of XXXI, formed via a C-3 hemiacetal) are the most feasible as both hexuloses should degrade in hot alkali by cleavage of the carbon backbone to yield small fragments (40).

Thermodynamic Functions of Activation

Since 1,5:3,6-dianhydro-D-galactitol is essentially the only product formed from cleavage of the oxygen-aglycon bond of 1,5-anhydrocellobiitol, in 2.5N NaOH at 170°C., the thermodynamic functions of activation for its production are representative of the oxygen-aglycon bond as a whole. The large enthalpy of activation (ΔH^* = 42.1 kcal./mole; Table VI) is consistent with an S_N1 mechanism and is comparable to the value observed for sodium methyl α-D-glucopyranosiduronate (ΔH^* = 40.0 kcal./mole) (23) which has been proposed to react by an S_N1 mechanism. As a further comparison, methyl α-D-glucopyranoside which has been proposed to undergo alkaline degradation by an $S_N1cB(6)$ mechanism, exhibits a much lower ΔH^*, 32.4 kcal./mole (23), and the glucosyl-glucose (G-G) glycosidic linkage of methyl β-cellobioside, which has been proposed to undergo alkaline degradation by an $S_N1cB(2)$ mechanism[12], has an enthalpy of activation of 35.4 kcal./mole (20).

The oxygen-aglycon bond in 1,5-anhydrocellobiitol exhibits an entropy of activation (ΔS^* = +7 e.u., Table VI) which is more negative than the entropy of activation of sodium methyl α-D-glucopyranosiduronate [S_N1; ΔS^* = +15 e.u. (23)] but which is still indicative of an S_N1 mechanism when compared to the entropies of activation of the G-G linkage in methyl β-cellobioside [$S_N1cB(2)$; ΔS^* = -2.7 e.u. (20)] and methyl α-D-glucopyranoside [$S_N1cB(6)$; ΔS^* = -14 e.u. (23)]. Thus,

[12] A single mechanism may be inadequate to describe alkaline degradation of methyl β-cellobioside. Thus, too much emphasis should not be put on this comparison.

the thermodynamic functions of activation indicate that the alkaline cleavage of the oxygen-aglycon bond proceeds by an S_N1 mechanism in 2.5N NaOH at 170°C.

In 0.5N NaOH (2.5F ionic strength) at 170°C. cleavage of the oxygen-aglycon bond yields both 1,5:3,6-dianhydro-D-galactitol and unidentified product(s). By adding the rates of formation of both products, the thermodynamic functions of activation[13] can be calculated for the cleavage of the oxygen-aglycon at 0.5N NaOH. The functions thus calculated are comparable (ΔH^* = 42.5 kcal./mole; ΔS^* = 8.5 e.u.) to the values obtained at 2.5N NaOH which indicates an S_N1 mechanism governs the cleavage of the oxygen-aglycon bond over the range of hydroxide ion concentration studied.

Effect of Ionic Strength at Constant Hydroxide Ion Concentration

Increasing ionic strength effects a sharp increase in the rate of alkaline cleavage of the oxygen-aglycon bond. On increasing the ionic strength from 0.5 to 2.5F at 0.5N NaOH the rate of cleavage of the oxygen-aglycon bond [represented by summation of the rate constants for the formation of 1,5:3,6-dianhydro-D-galactitol and the unidentified product(s), k_{OA}] increased 64% (from 5.3×10^{-7} sec.$^{-1}$ to 8.7×10^{-7} sec.$^{-1}$; Table III). The positive "salt effect" observed is indicative of an S_N1 mechanism, particularly since an $S_N1cB(3)$ mechanism would be expected to exhibit a negative "salt effect." Bateman, et al. (41) have reported a 50% increase in the rate of hydrolysis of p,p'-dimethylbenzhydryl chloride in 85% aqueous actone (S_N1 mechanism) with the addition of small amounts (0.051N) of salt. The significantly larger change in ionic strength required in the 1,5-

[13]The rate constants for formation of unidentified product(s) are not known with as high a precision as the other rate constants, hence the values of the thermodynamic functions calculated incorporating them are also of a lower precision.

anhydrocellobiitol system to affect a 50-60% increase in the rate of reaction is probably due to a "leveling effect" of the polar aqueous system.

Increasing ionic strength also causes a significant change in the product distribution from oxygen-aglycon bond cleavage. As the ionic strength is increased from 0.5 to 2.5F at 0.5N NaOH, the proportion of unidentified products increases from about 26% to about 54% of the products formed as a result of oxygen-aglycon bond cleavage (Table III). This is consistent with an S_N1 mechanism in which increased ionic strength effects increased stabilization, i.e., longer average lifetime of the initial C-4 carbonium ion (XXVII, Fig. 21). Increasing stability or stabilization of a carbonium ion increases its selectivity as to the mode of reaction (39). Intramolecular reaction of (XXVII) to yield 1,5:3,4-dianhydro-D-galactitol (XXIV) and ultimately 1,5:3,6-dianhydro-D-galactitol (XXI) could involve nucleophilic attack at the C-4 cation by either the C-3 hydroxyl or the C-3 alkoxy anion. However, the shift toward a larger proportion of 1,5:3,6-dianhydro-D-galactitol as the hydroxide ion concentration increases (Table III) implies that the C-3 alkoxy anion is much more effective in trapping the C-4 carbonium ion than is the nonionized C-3 hydroxyl. As the ionic strength increases, the effect on the concentration of nucleophile (C-3 alkoxy anion) would be small relative to the additional stabilization of the initial C-4 carbonium ion. The resultant longer average-lifetime of the C-4 carbonium ion could allow a significant amount of carbonium ion rearrangement (leading to unidentified products) to take place.

Effect of Hydroxide Ion Concentration at Constant Ionic Strength

Since cleavage of the oxygen-aglycon bond does not result in formation of 1,5-anhydro-D-glucitol, pseudo-first-order rate constants, k_{OA}, (Table X) for

the bond cleavage can be calculated from Equation (9) in conjunction with Equation (30).

$$C_{OA,t} - C_{OA_o} = (k_{OA}\, C_{AC_o}/k_r)[1 - \exp(-k_r t)] \qquad (9)$$

$$C_{OA,t} = (C_{AC_o} + C_{AG_o}) - (C_{AC,t} + C_{AG,t}) \qquad (30)$$

where $C_{OA,t}$ = concentration of products from cleavage of oxygen-aglycon bond at time t, mole/liter,

$C_{AC,t}$ = concentration of reactant at time t, mole/liter,

$C_{AG,t}$ = concentration of 1,5-anhydro-D-glucitol at time t, mole/liter,

C_{OA_o} = concentration of products from cleavage of oxygen-aglycon bond at $t = 0$, mole/liter,

C_{AC_o} = concentration of reactant at $t = 0$, mole/liter,

C_{AG_o} = concentration of 1,5-anhydro-D-glucitol at $t = 0$, mole/liter,

k_{OA} = pseudo-first-order specific rate constant for oxygen-aglycon bond cleavage, $sec.^{-1}$, and

k_r = pseudo-first-order specific rate constant for reactant disappearance, $sec.^{-1}$.

Alternately, the value of k_{OA} (Table X) can be calculated from Equation (31)

$$k_r - k_{AG} = k_{OA}. \qquad (31)$$

The pseudo-first-order rate constant for cleavage of the oxygen-aglycon bond exhibits a negative dependence on the hydroxide ion concentration (Table X); the reaction order[14] with respect to hydroxide ion, b, (Fig. 23) is approximately -0.3.

[14]From Equation (3) $k_r = k[^-OH]^b$, hence $\ln k_r = \ln k + b \ln [^-OH]$.

TABLE X

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE HETEROLYSIS OF THE OXYGEN-AGLYCON BOND AT 170°C.

NaOH, N	NaTOS, F	k_{-OA}[a] x 10^6, $sec.^{-1}$	k_{-OA}[b] x 10^6, $sec.^{-1}$	k_{-OA}[c] x 10^6, $sec.^{-1}$
2.5	0.0	0.58[d] ± 0.12[e]	0.54	1.06
1.5	1.0	0.53 ± 0.11	0.64	1.52
1.0	1.5	0.82 ± 0.11	0.74	N.D.[f]
0.5	2.0	0.85 ± 0.13	0.89	0.53

[a] Calculated from Equations (9) and (30); method of least squares; 1,5-anhydrocellobiitol.

[b] Calculated from Equation (31) using values of k_{-r} and k_{-AG} from the empirical correlation of k vs. ln OH (Fig. 6); 1,5-anhydrocellobiitol.

[c] Calculated from Equation (31) and Table VIII; 1,5-anhydro-2,3,6-tri-O-methylcellobiitol.

[d] Average of three values.

[e] The standard deviation determined is large because the variation in concentration of both 1,5-anhydrocellobiitol ($C_{-AC,t}$) and 1,5-anhydro-D-glucitol ($C_{-AG,t}$) is on the order of the value of $C_{-OA,t}$ [see Equation (30)], hence the value of $C_{-OA,t}$ can vary quite widely.

[f] N.D. = not determined.

The inverse relationship of the rate constant, k_{-OA}, and hydroxide concentration is consistent with an S_N1 mechanism if the "leaving ability" of the glycon (the glucopyranosyloxy anion) is inversely proportional to the hydroxide ion concentration. The rate of an S_N1 mechanism should be independent of the nucleophile concentration and, hence, the rate should remain constant if the ionic strength and the leaving group remain constant (14,30). However, as the hydroxide ion concentration increases, the hydroxyl groups of the reactant will ionize. When ionization occurs on the leaving group the "leaving ability" should be decreased since stabilization or delocalization of the negative

charge created during cleavage of the oxygen-aglycon bond will be hindered by the presence of a net negative charge prior to the oxygen-aglycon bond cleavage. Ionization of hydroxyl(s) on the leaving group prior to oxygen-aglycon bond cleavage may be so detrimental to the "leaving ability" of the glucosyloxy group that essentially no cleavage occurs. The rate constant would then appear to be depressed as the hydroxide ion concentration increases because the effective concentration of the reactant (i.e., nonionized species) will be lower than that used in the calculation of the rate constant. However, it should be noted that

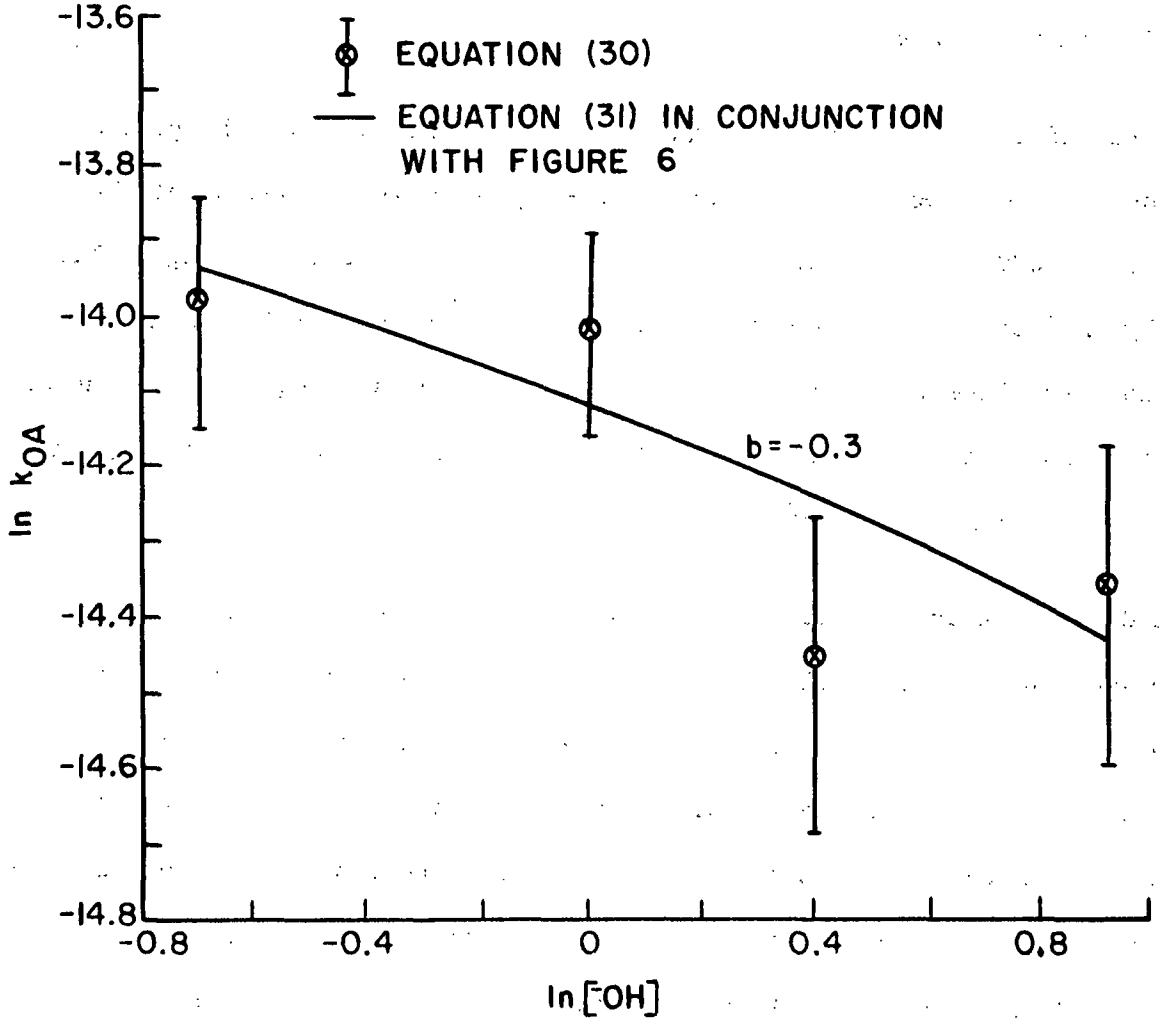


Figure 23. The Determination of the Empirical Reaction Order with Respect to Hydroxide Ion Concentration for the Heterolysis of the Oxygen-Aglycon Bond in 1,5-Anhydrocellobiitol (0.1M) at 170°C.

the pyranose ring alkoxy anions are at least 10 times more basic than is the glucopyranosyloxy anion (42). Therefore, initiation of oxygen-aglycon bond cleavage would tend to drive the equilibrium for the ionization of secondary hydroxyls toward the nonionized hydroxyl and thus reduce the effect of ionization on the "leaving ability" of the leaving group.

Ionization of hydroxyl groups on the aglycon of 1,5-anhydrocellobiitol (the portion of the molecule which is the precursor to the C-4 carbonium ion) should help stabilize the developing C-4 carbonium ion. Thus, on this basis, the rate of oxygen-aglycon bond cleavage should increase with increasing hydroxide ion concentration.

The net effect of increasing hydroxide ion concentration on the pseudo-first-order rate constant for cleavage of the oxygen-aglycon bond should be the sum of the effect of ionization of hydroxyl groups on the "leaving ability" of the glycon (negative) and on stabilization of the carbonium ion forming in the aglycon (positive). Since the rate constant exhibits a negative dependence on hydroxide ion concentration, the effect of base on the "leaving ability" of the glucopyranosyloxy group must dominate.

Based on the above discussion, oxygen-aglycon bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (XXXVI) should exhibit a more drastic negative dependence on alkali concentration than 1,5-anhydrocellobiitol. In the methylated derivative (XXXVI) ionization in the aglycon and, thus, potential stabilization of the forming C-4 carbonium, cannot occur. Therefore, there would be no counteraction to the negative effect of alkali on the "leaving ability" of the glucopyranosyloxy anion. Unfortunately, the meager data available for the methylated derivative (Table X) are very scattered and seem to indicate a

positive dependence of k_{OA} on hydroxide ion concentration. The significance of the positive dependence of k_{OA} on hydroxide ion concentration, or whether it is even real[15], is not known.

The arguments proposed regarding "leaving ability" as a function of hydroxide ion concentration can also be applied to an $S_N1cB(3)$ mechanism governing oxygen-aglycon bond cleavage in 1,5-anhydrocellobiitol. However, for this to be the case, the effect of ionization on the leaving group (negative) would have to grossly overshadow the requisite ionization of the C-3 hydroxyl group (positive), i.e., the order with respect to hydroxide ion concentration must decrease from a theoretical value of +1.0 to an observed value of -0.3.

Assuming that the alkaline cleavage of the oxygen-aglycon bond proceeds by an S_N1 mechanism, the degree of ionization of the hydroxyl groups on the carbonium appears to have a profound effect on the product ratio between substitution (production of 1,5:3,6-dianhydrogalactitol) and rearrangement [production of the unidentified product(s)]. In 2.5N sodium hydroxide all the 1,5-anhydro-4-deoxy-xylo-hexitol-4-cation is converted to 1,5:3,6-dianhydro-D-galactitol while in 0.5N sodium hydroxide (ionic strength maintained at 2.5F) only 46% of the carbonium ion is converted to 1,5:3,6-dianhydrogalactitol. This suggests that at low hydroxide ion concentrations and comparable ionic strength, the life expectancy of the carbonium ion is long enough, presumably due to less C-3 ionization, to allow the rearrangement reactions to become significant.

[15]Based on the above correlation, the value of k_r for 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol at 0.5N NaOH and 2.0N NaTOS is suspect. If the value in Table X is in error and the true value is actually greater, then the dependence of k_{OA} on hydroxide ion concentration may in fact be negative. There is no known reason, however, for the determined value to be in error.

CONCLUSIONS REGARDING THE MECHANISM OF OXYGEN-AGLYCON BOND CLEAVAGE

The data observed for the alkaline cleavage of the oxygen-aglycon bond in 1,5-anhydrocellobiitol indicates that the cleavage proceeds by an S_N1 mechanism exclusively (Fig. 21).

The thermodynamic functions of activation of the alkaline cleavage of the oxygen-aglycon bond furnish strong evidence for an S_N1 mechanism, particularly the high enthalpy of activation (ca. 42 kcal./mole) observed. The increase in the pseudo-first-order rate constant for oxygen-aglycon bond cleavage with an increase in ionic strength is also strong evidence for an S_N1 mechanism. The effects of hydroxide ion concentration on the pseudo-first-order rate constant and product distribution are consistent with an S_N1 mechanism in the oxygen-aglycon bond cleavage in 1,5-anhydrocellobiitol. In terms of carbonium ion stability the heterolysis of the oxygen-aglycon bond to yield a C-4 carbonium ion would be considered highly unlikely. The question then naturally arises as to why such a heterolysis should take place. It should be remembered that the transition state free energy for the heterolysis is related to both the ability of the system to delocalize the positive charge developing on the carbon atom (indicated by the stability of the resultant carbonium ion) and the ability of the oxygen atom of the fragmenting species to accept the pair of electrons from the cleaving bond ("leaving ability"). The leaving ability of the species can be roughly correlated with its basicity (the weaker the base the better the leaving group). The D-glucopyranosyloxy anion is a very weak base relative to alkoxy anions usually formed in glycosidic bond cleavage. Hence, the D-glucopyranosyloxy anion would be a much better leaving group than is usually encountered. Thus, the leaving ability of the D-glucopyranosyloxy anion can be

thought to decrease the transition state free energy of the oxygen-aglycon bond heterolysis to the extent that it can compete effectively with glycosyl-oxygen bond cleavage.

CLEAVAGE OF THE GLYCOSYL-OXYGEN BOND

POSSIBLE MECHANISMS FOR CLEAVAGE AT THE GLYCOSYL-OXYGEN BOND

Three reaction mechanisms are considered to be possible for glycosyl-oxygen bond cleavage: S_N1, $S_N1cB(2)$, and $S_N1cB(4)$. These potential mechanisms will be described briefly and then discussed as to their ability to account for the available experimental data. The results of this study do not indicate that glycosyl-oxygen bond cleavage is governed exclusively by either an S_N1 or S_N1cB mechanism but rather that both types of mechanisms are functioning simultaneously.

Potential $S_N1cB(2)$ Mechanism

The $S_N1cB(2)$ [McCloskey-Coleman (8)] mechanism as it pertains to the alkaline degradation of 1,5-anhydrocellobiitol, is shown in Fig. 24. A rapid equilibrium between the C-2' hydroxyl and the C-2' alkoxy anion of 1,5-anhydrocellobiitol (XIX-XIXa) precedes the rate determining, nucleophilic attack of the C-2' alkoxy anion at C-1' which yields 1,2-anhydro-α-D-glucopyranose (II) and 1,5-anhydro-D-glucitol (XX). 1,2-Anhydro-α-D-glucopyranose can subsequently react via a nucleophilic attack at C-1 by either the C-6 alkoxy anion to yield 1,6-anhydro-β-D-glucopyranose (III), or hydroxide ion to yield D-glucopyranose (IV) which will degrade rapidly. Possible nucleophilic participation by the C-3 alkoxy anion in the degradation of the 1,2-epoxide has been mentioned, but not investigated by Janson and Lindberg (22). If nucleophilic attack of the trans-diaxial C-3 alkoxy anion at C-2 of the 1,2-anhydro-α-D-glucopyranoside (1C conformation) occurs epoxide migration to form 2,3-anhydro-D-mannopyranose (XXXVII) would

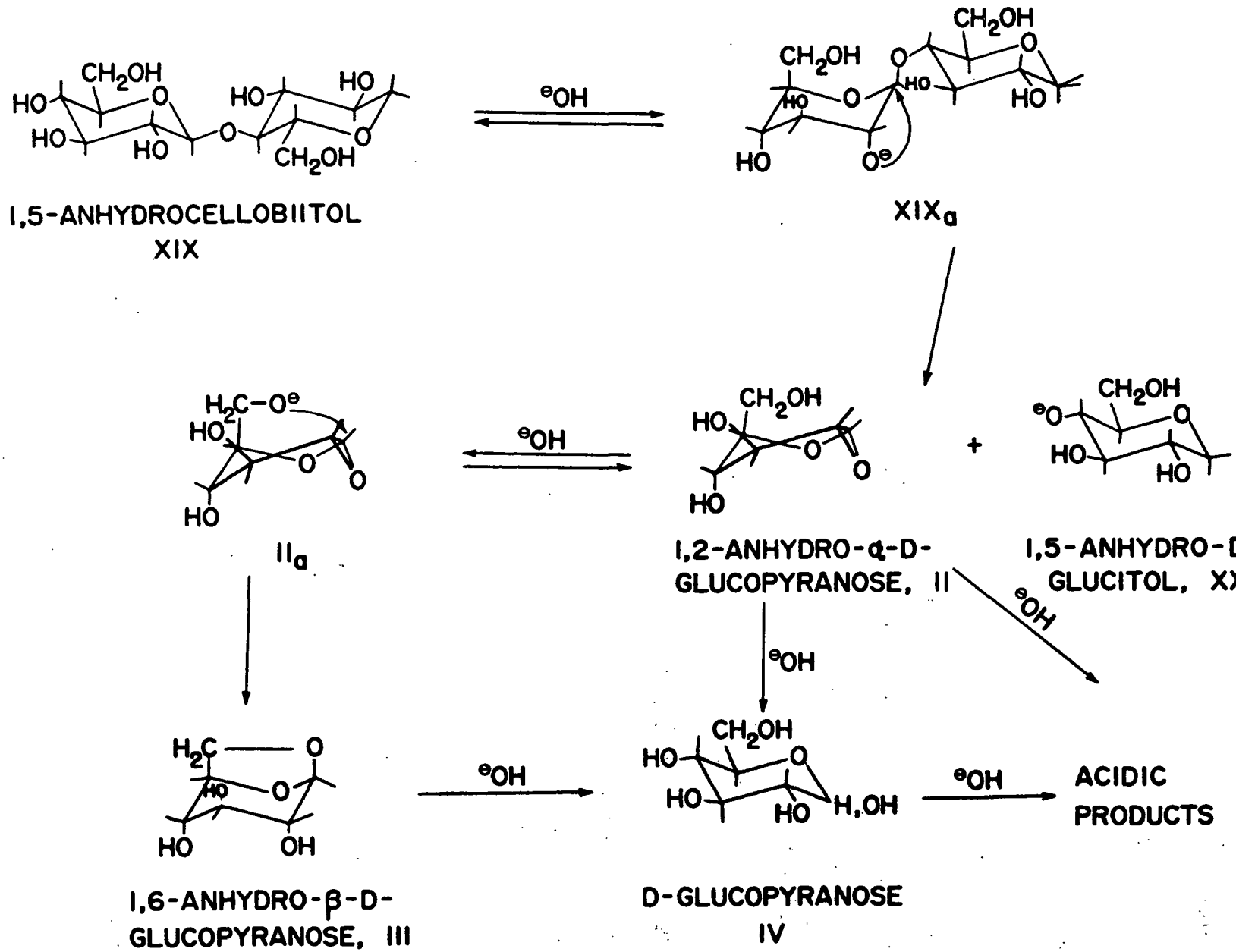


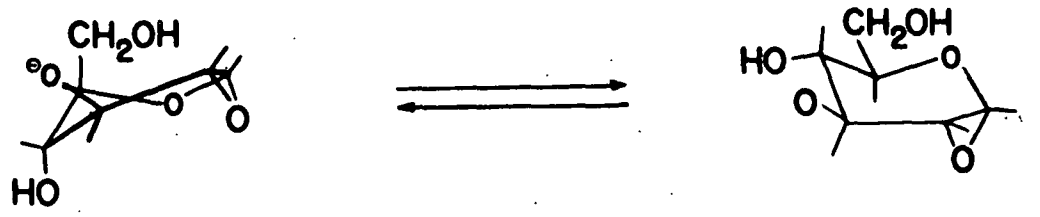
Figure 24. Potential $S_N1cB(2)$ Mechanism for Alkaline Degradation of the Glycosyl-Oxygen Bond in 1,5-Anhydrocellobiitol

result (Fig. 25). A similar migration involving the C-4 alkoxy anion (1C conformation) would result in formation of 3,4-anhydro-D-altropyranose (XXXVIII). In order to achieve the requisite trans-diaxial configuration for the reverse migration, the pyranose ring must revert to the C1 conformation (Fig. 25). Once the epoxide has migrated from the 1,2-position (i.e., formation of 2,3-anhydro-mannopyranose or 3,4-anhydro-D-altropyranose), a reducing sugar is formed which should rapidly degrade, presumably via β-alkoxy elimination.

Based on the work done with phenyl glucosides at lower temperatures, nucleophilic attack at C-1 by the C-6 alkoxy anion to yield 1,6-anhydro-β-D-glucopyranose would be expected to be the predominant alkaline reaction of 1,2-anhydro-α-D-glucopyranose. However, as discussed above, other nucleophiles are present and at the more severe conditions associated with 1,5-anhydrocellobiitol degradation the potential exists for a significantly different product distribution. Thus, the yield of 1,6-anhydro-β-D-glucopyranose from 1,2-anhydro-α-D-glucopyranose may be significantly reduced.

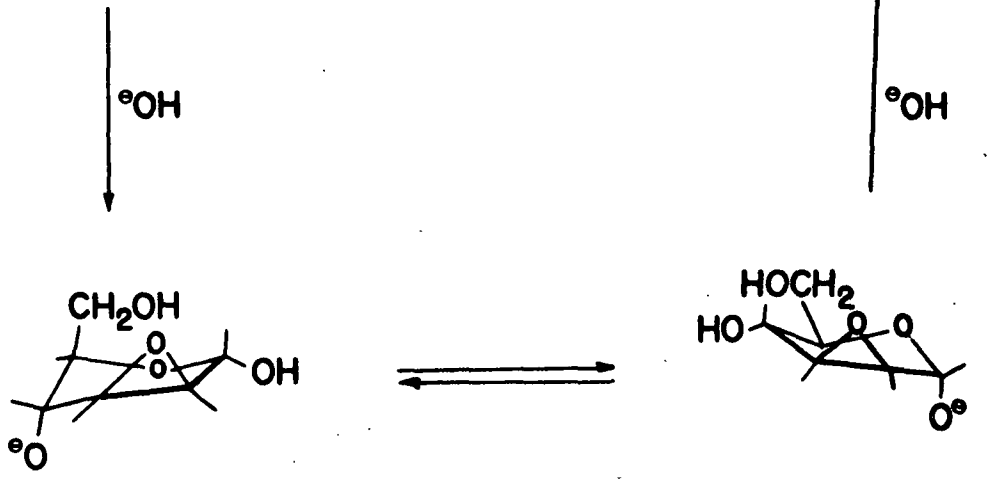
Potential $S_N1cB(4)$ Mechanism

An $S_N1cB(4)$ mechanism similar to that proposed by Capon (13) for the alkaline degradation of phenyl β-D-mannopyranoside (Fig. 3) can potentially occur in the alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol (Fig. 26). A rapid equilibrium between the C-4' hydroxyl and the C-4' alkoxy anion of 1,5-anhydrocellobiitol (XIX-XIXa) precedes the rate-determining, nucleophilic attack of the C-4' alkoxy anion at C-1' which yields 1,4-anhydro-α-D-glucopyranose (XXXIX) and 1,5-anhydro-D-glucitol (XX). 1,4-Anhydro-α-D-glucopyranose can subsequently react via either heterolysis or bimolecular nucleophilic substitution. Heterolysis of XXXIX would yield the D-glucopyranosyl-



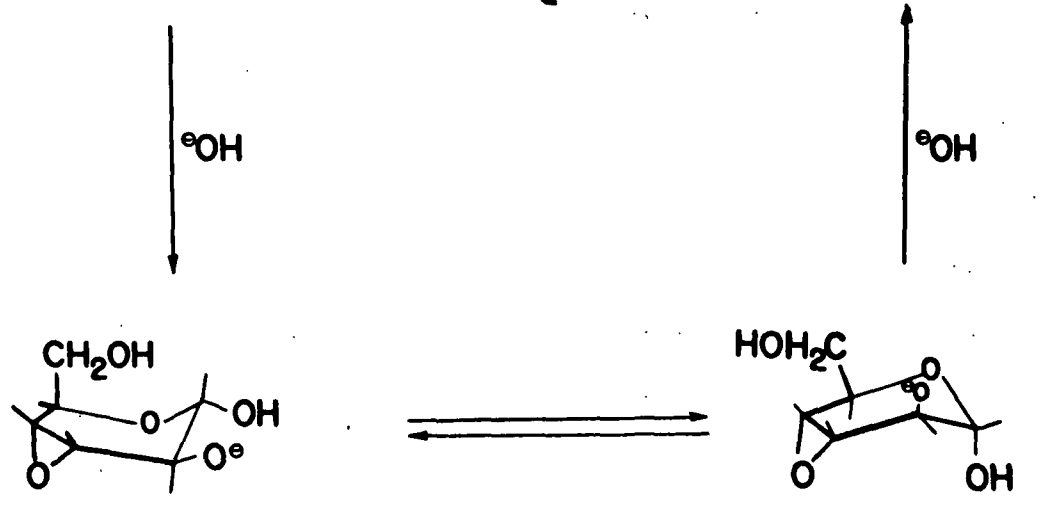
1,2-ANHYDRO-α-D-GLUCOPYRANOSE

II_a



2,3-ANHYDRO-D-MANNOPYRANOSE

$XXXVII_a$



3,4-ANHYDRO-D-ALTROPYRANOSE

$XXXVIII_a$

Figure 25. Potential Oxirane Ring Migration in Alkaline Degradation Products of 1,5-Anhydrocellobiitol

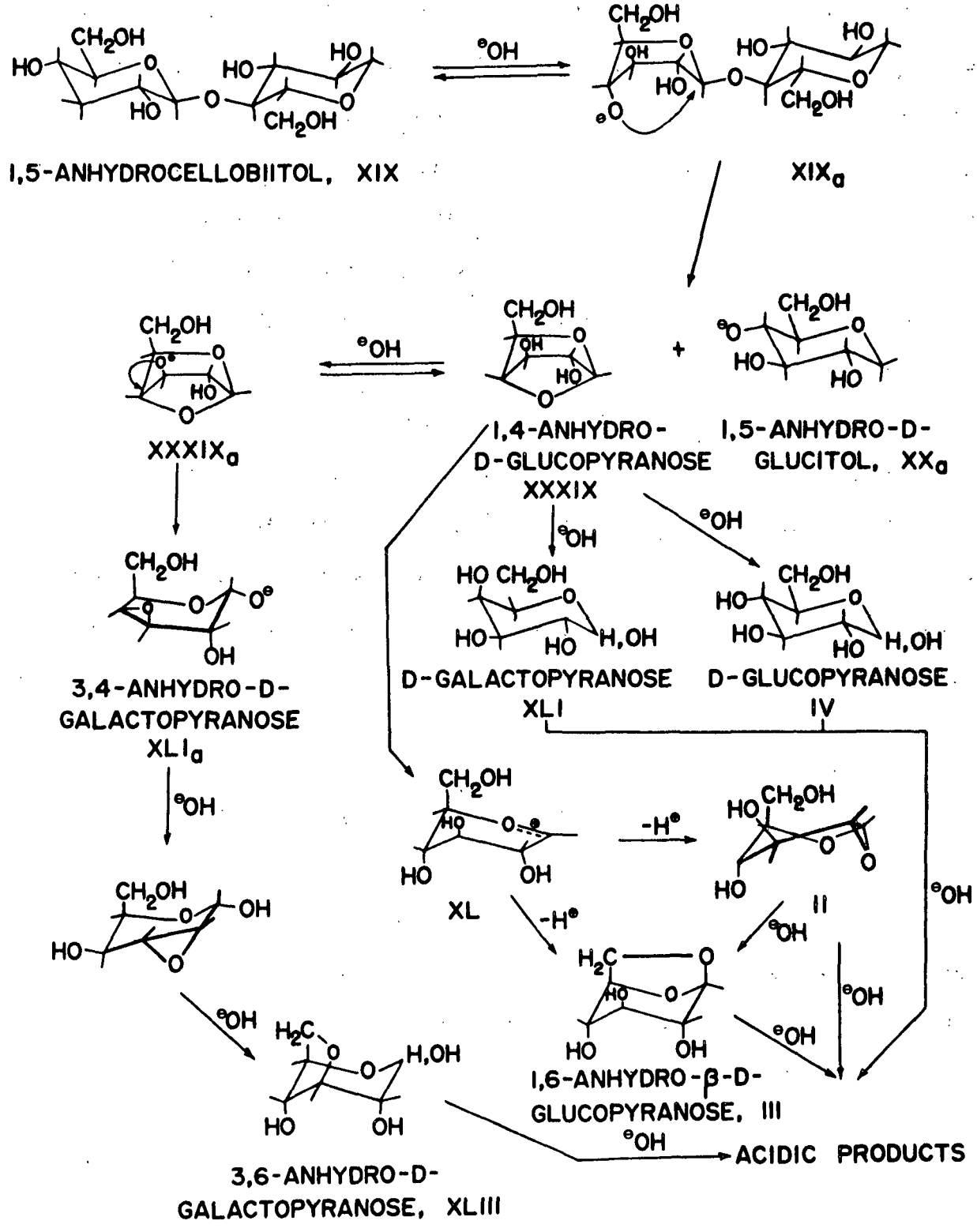


Figure 26. Potential $S_N1cB(4)$ Mechanism for the Alkaline Degradation of 1,5-Anhydrocellobiitol

cation (XL) which is stabilized by resonance with the ring oxygen (13); hence, its half-life may be such that it will show some selectivity between nucleophiles (38). Thus, the D-glucopyranosyl-cation (XL) can potentially form D-glucopyranose (IV) by reacting with hydroxide ion or undergo intramolecular reactions involving the C-6 or C-2 alkoxy anions to form 1,6-anhydro-β-D-glucopyranose (III) or 1,2-anhydro-α-D-glucopyranose (II), respectively. 1,2-Anhydro-α-D-glucopyranose will react further as previously discussed to yield 1,6-anhydro-β-D-glucose or acidic products. 1,4-Anhydro-α-D-glucopyranose can potentially undergo nucleophilic attack by hydroxide ion at either C-1 or C-4 to yield D-glucopyranose (IV) or D-galactopyranose (XLI), respectively. An intramolecular nucleophilic attack by the trans-diaxial C-3 alkoxy anion at C-4 would yield 3,4-anhydro-D-galactopyranose (XLII) which can either degrade directly via β-alkoxy elimination or undergo a series of intramolecular displacement reactions to yield 3,6-anhydro-D-galactopyranose (XLIII) which will then degrade rapidly via β-alkoxy elimination.

Potential S_N1 Mechanism

The possible S_N1 mechanism for the alkaline cleavage of the glycosyl-oxygen bond in 1,5-anhydrocellobiitol is shown in Fig. 27. This mechanism is similar to that proposed for phenyl β-D-mannopyranoside (7) (Fig. 2). The heterolysis of the glycosyl-oxygen bond results in the formation of 1,5-anhydro-D-glucitol (XX) and D-glucopyranosyl-cation (XL). Reactions of the D-glucopyranosyl-cation which yield 1,6-anhydro-β-D-glucopyranose or acidic products have been discussed previously.

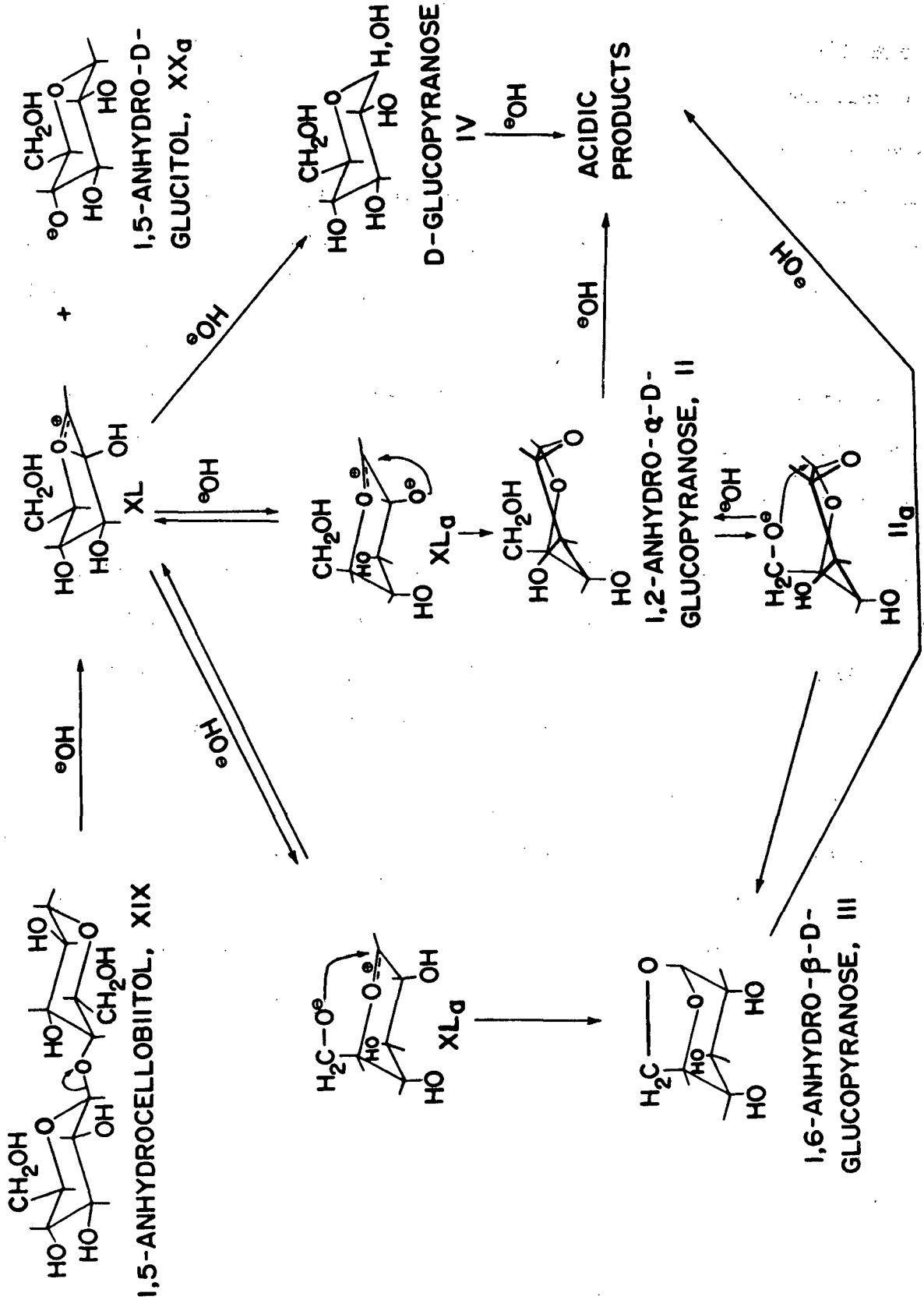


Figure 27. Potential S_N1 Mechanism for Degradation of Glycosyl-Oxygen Bond in 1,5-Anhydrocellobiitol

COMPARISON OF OBSERVED DATA WITH POTENTIAL MECHANISMS

Product Analysis

In discussing cleavage of the oxygen-aglycon bond in 1,5-anhydrocellobiitol it was concluded that essentially no 1,5-anhydro-D-glucitol is produced. Hence, the production of 1,5-anhydro-D-glucitol is characteristic of cleavage of the glycosyl-oxygen bond and the pseudo-first-order rate constant for appearance of 1,5-anhydro-D-glucitol can be taken as a direct measure of glycosyl-oxygen bond cleavage in 1,5-anhydrocellobiitol. However, quantitative formation of 1,5-anhydro-D-glucitol for glycosyl-oxygen bond cleavage would be predicted from any of the potential reaction mechanisms and hence its formation is of no value for discerning between the possible mechanisms.

Similarly, the formation of 1,6-anhydro-β-D-glucopyranose can feasibly be accounted for by any one of the potential reaction mechanisms. However, the amount of 1,6-anhydro-β-D-glucopyranose formed from glycosyl-oxygen bond cleavage would be expected to be dependent on the reaction mechanism.

Since 1,6-anhydro-β-D-glucopyranose can be formed only as a result of glycosyl-oxygen bond cleavage, the mole fraction of 1,6-anhydro-β-D-glucopyranose formed based on the overall degradation of 1,5-anhydrocellobiitol ($X_{L,\infty}$; Tables II and VIII) could be misleading. Therefore, the $X_{L,\infty}$ values have been converted to mole fractions based only on glycosyl-oxygen bond cleavage ($Y_{L,\infty}$). The $Y_{L,\infty}$ values for degradations of 1,5-anhydrocellobiitol and its 2,3,6-tri-*O*-methyl analog are shown in Table XI.

TABLE XI

THE RELATIVE AMOUNT OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE FORMED DURING THE ALKALINE DEGRADATION OF THE GLYCOSYL-OXYGEN BOND AT 170°C.

NaOH, N	NaTOS, F	1,5-Anhydrocellobiitol Levoglucosan Formed, $Y_{L,\infty}$	1,5-Anhydro-2,3,6-tri-O-methyl Cellobiitol Levoglucosan Formed, $Y_{L,\infty}$
2.5	0.0	0.35	0.73
1.5	1.0	0.36	0.85
1.0	1.5	0.36	N.D.[a]
0.5	2.0	0.32	0.63

[a] N.D. = not determined.

The formation of 1,6-anhydroglucopyranoses during the alkaline degradation of trans-1,2-α-glycosides has historically been associated with an $S_N1cB(2)$ mechanism (8,20). In particular, under the "mild" conditions (100°C.; 1.3N alkali) required for the alkaline degradation of phenyl β-D-glucopyranoside, 1,6-anhydro-β-D-glucopyranose can be isolated in high yield (88%) (8). Therefore, the much lower "yield" of 1,6-anhydro-β-D-glucopyranose observed in the alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol (ca. 35%, Table XI) can be taken to indicate either that multiple mechanisms are governing the alkaline cleavage of the glycosyl-oxygen bond or that competing reactions which lead to acid products from 1,2-anhydro-α-D-glucopyranose (Fig. 24 and 25) become more significant as the temperature increases. The latter explanation, however, seems unrealistic in light of the relatively high "yield" of 1,6-anhydro-β-D-glucopyranose from the alkaline cleavage of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (ca. 70%, Table XI). The only obvious difference between the two compounds is the ability of the aglycon to become negatively

charged due to hydroxyl ionization in the case of 1,5-anhydrocellobiitol but not in tri-O-methyl-1,5-anhydrocellobiitol (XXXVI). Since the difference in the "yield" of 1,6-anhydro-β-D-glucopyranose (III) from tri-O-methyl-1,5-anhydrocellobiitol relative to 1,5-anhydrocellobiitol does not appear to be a function of the hydroxide ion concentration, it would appear that the alkaline dependence of the "leaving ability" of the aglycon of 1,5-anhydrocellobiitol[16] is not a significant factor in the difference in the yield of III. Hence, the difference in "yield" of III between the methylated and unmethylated disaccharide would appear to be due to a mechanistic shift toward the $S_N1cB(2)$ mechanism in the tri-O-methyl-1,5-anhydrocellobiitol. The reason for such a mechanistic shift, however, is not known. Since the 70+% calculated "yield" of 1,6-anhydro-β-D-glucopyranose from the tri-O-methyl-1,5-anhydrocellobiitol is reasonably close to the crystalline yields obtained from phenyl β-D-glucopyranoside, it is possible that the tri-O-methyl-1,5-anhydro-cellobiitol reacts solely by an $S_N1cB(2)$ mechanism. If such is the case, then cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol is governed by the $S_N1cB(2)$ mechanism no more than 50% of the time and possibly less because of potential 1,6-anhydro-β-D-glucopyranose formation through an S_N1 or $S_N1cB(4)$ mechanism.

Thermodynamic Functions of Activation

The magnitudes of the thermodynamic functions of activation for the potential mechanisms involved in the alkaline cleavage of glycosidic linkages are not well defined. This is primarily due to the fact that the mechanisms for the few potential reference compounds available (Table XII) have not been

[16]When the aglycon contains ionizable hydroxyls, increased hydroxide ion concentration results in increased ionization of the aglycon and hence in a decreased "leaving ability" of the aglycon. See discussion in "Effect of Hydroxide Ion Concentration at Constant Ionic Strength" under cleavage of the oxygen-aglycon bond, p. 72.

established conclusively. The lack of good reference data severely limits the conclusions which can be drawn from the thermodynamic data.

TABLE XII

THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE ALKALINE DEGRADATION OF VARIOUS COMPOUNDS IN 2.5N SODIUM HYDROXIDE AT 170°C.

Compound	Reference	Proposed Mech. for Degradation	E_A, kcal./mole	ΔH^*, kcal./mole	ΔS^*, cal./°K mole	ΔF^*, kcal./mole
Methyl α-D-glucoside	23	$S_N1cB(6)$	33.3	32.4	-13.6	38.4
Methyl β-D-glucoside	20	$S_N1cB(2)$	37.6	36.7	-2.7	38.0
Glucosyl-methyl glucoside linkage of methyl β-cellobioside	20	$S_N1cB(2)$	36.3	35.4	-2.7	36.6
Sodium methyl α-D-glucosiduronate	23	S_N1	40.9	40.0	+14.7	33.5
1,5-Anhydrocellobiitol[a]						
A) Oxygen-aglycon bond		S_N1	42.6	41.7	+6.9	38.6
B) Glycosyl-oxygen bond		?	38.0	37.1	+1.0	36.7

[a]This work.

The thermodynamic functions of activation for cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol are similar in magnitude to those for the glycosyl-methyl glucoside linkage in methyl β-cellobioside (Table XII). Best (20) concluded that the alkaline degradation of methyl β-cellobioside was consistent with an $S_N1cB(2)$ mechanism. However, there is nothing in Best's data which is inconsistent with a multiple mechanism. Thus, the possibility of a mixed mechanism in methyl β-cellobioside is quite real and its use as a reference compound for a $S_N1cB(2)$ mechanism would not appear to be appropriate.

Since an $S_N1cB(2)$ reference reaction is not available, comparisons between an $S_N1cB(6)$ and S_N1 mechanism can potentially be enlightening. However, there is the question as to how the thermodynamic functions of activation of an $S_N1cB(2)$ or $S_N1cB(4)$ mechanism are related to those of an $S_N1cB(6)$ mechanism. Since this relationship is not clear, conclusions based on such data would necessarily be speculative.

The thermodynamic functions of activation of methyl α-D-glucopyranoside and sodium methyl α-D-glucopyranosiduronate, relative to each other at least, are typical of the differences which might be expected between S_N1cB and S_N1 mechanisms[17] (Table XII). Robins (23) has proposed an S_N1 mechanism for the alkaline degradation of methyl α-D-glucopyranosiduronate and the similarity of the thermodynamic functions of activation (Table XII) for it and the cleavage of the oxygen-aglycon bond of 1,5-anhydrocellobiitol (proposed S_N1 mechanism) lends credence to their use as reference reactions for an S_N1 mechanism. While the alkaline degradation of methyl α-D-glucopyranoside has been proposed to proceed by an $S_N1cB(6)$ (23) mechanism, the mechanism has not been demonstrated conclusively. Conversely, no data are available which refutes an $S_N1cB(6)$ mechanism in the alkaline degradation of methyl α-D-glucopyranoside.

The observed thermodynamic functions for the cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol are intermediate between the thermodynamic function of activation for methyl α-D-glucopyranoside [$S_N1cB(6)$] and sodium methyl α-D-glucopyranosiduronate (S_N1) (Table XII). Thus, on this

[17]This is assuming, as Robins (23) did, that the similarity of the S_N2 to the S_N1cB mechanism allows an extension of the conclusions of Brown and Hudson (31) concerning S_N1 *vs.* S_N2 mechanisms.

basis, cleavage of the glycosyl-oxygen bond is consistent with a multiple mechanism.

It should be noted that if multiple mechanisms are functioning it might be expected that the Arrhenius correlation (i.e., ln k vs. $1/T$) would exhibit some curvature due to a changing proportion of mechanism type with changing temperature. The severity of this curvature would be related to the difference in ΔH^* for the different mechanisms. No such curvature was noted in the data for 1,5-anhydrocellobiitol but only a 20°C. temperature range was involved, and perhaps over a more extended temperature range such curvature might be observed.

Effect of Hydroxide Ion Concentration at Constant Ionic Strength

The reaction order with respect to the hydroxide ion concentration for the alkaline cleavage of the glycosyl-oxygen bond in 1,5-anhydrocellobiitol is a function of the hydroxide ion concentration, varying from 0.69 at 0.5N NaOH to 0.30 at 2.5N NaOH (Fig. 11). A similar function was observed by Best (20) for the glycosyl-methyl glucoside linkage in methyl β-cellobioside but not for methyl β-D-glucoside or the equivalent linkage in methyl β-cellobioside. Since Best did not control the total ionic strength of the reaction mixture, the source of the above effect could not be ascertained. In this study the ionic strength was held constant; thus several of the potential explanations for the observed curvilinear nature of the ln k vs. ln (OH) plot (20) are no longer valid.

Two possible explanations for the curvilinear nature of the ln k vs. ln ($^-$OH) plot (Fig. 11) will be considered. The first is the least likely and involves nucleophilic attack by the C-6 alkoxy anion (XIXa) (C1 conformation) at C-1' (1C conformation) (Fig. 28) to yield a 1,6-α-linked disaccharide

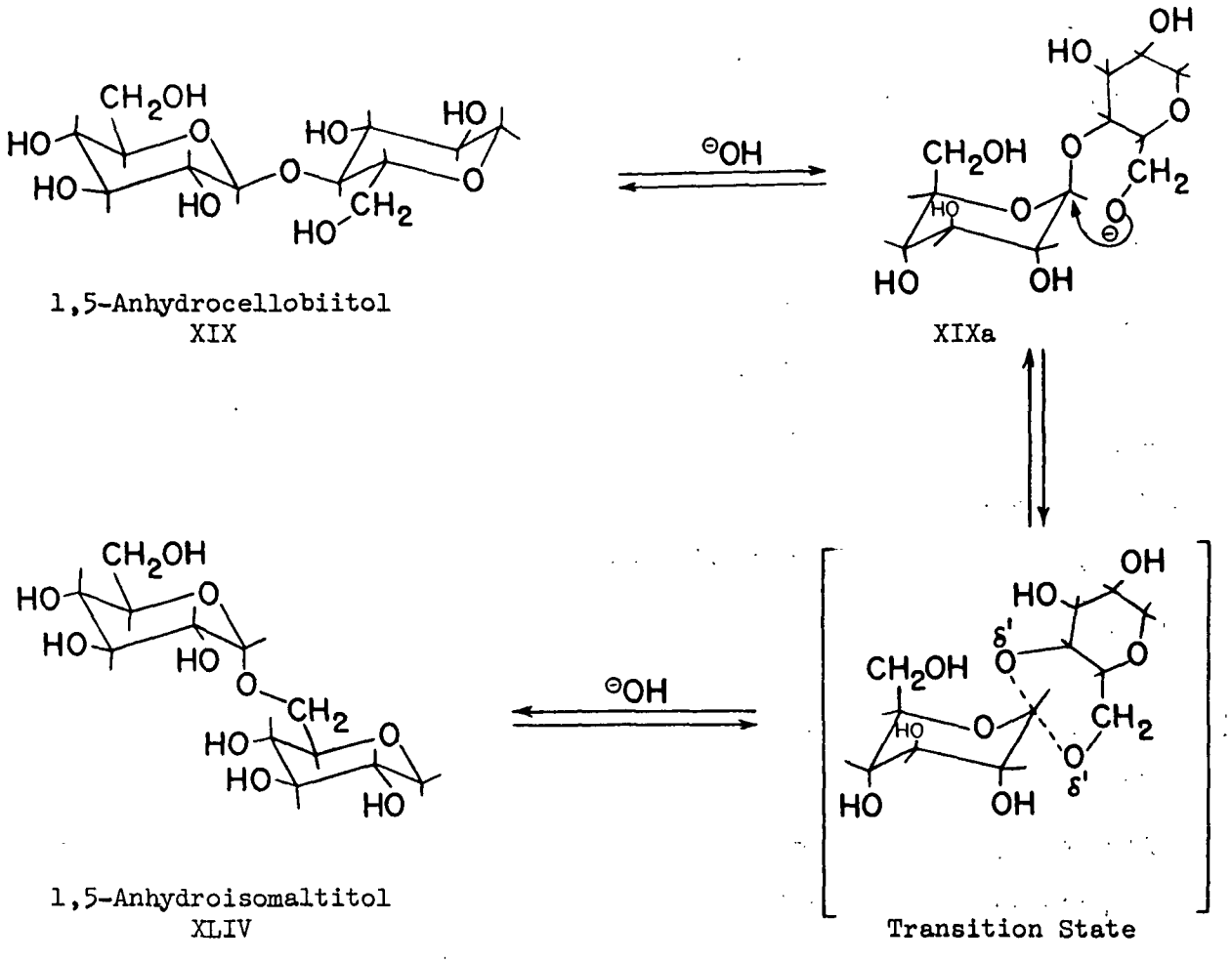


Figure 28. Possible Alkaline Reaction Mechanism in 1,5-Anhydrocellobiitol

XLIV (1,5-anhydro-6-O-(α-D-glucopyranosyl)-D-glucitol:1,5-anhydroisomaltitol). If such a reaction were to occur, it would compete with other degradation reactions but the resultant disaccharide probably would not be detected by the normal GLC analysis procedures. Presumably, the above reaction would become more important at higher alkali levels due to more C-6 hydroxyl ionization, thus causing the observed depression in the reaction order with respect to hydroxide (Fig. 11). Since α-linked disaccharides would be expected to degrade more slowly than β-linked disaccharides and a significant proportion of the reaction would need to proceed by this route to effect the depression in rate observed, the fact that no α-linked disaccharides could be formed by NMR analysis

of the reaction mixture indicates that this is not a viable explanation for the curvilinear nature of the ln k vs. ln (OH) plot.

The second possible explanation, which seems quite likely, involves the inverse relationship between the "leaving ability" of the leaving group and hydroxide ion concentration. The reasons for this inverse relationship have been discussed previously[18].

In order to determine the effect of ionization in the aglycon on the rate of alkaline degradation, a compound (1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol; XXXVI) in which the aglycon cannot become ionized was subjected to alkaline degradation. The reaction order with respect to hydroxide ion concentration for the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol is constant (0.66) (Fig. 15). Thus, when ionization is prohibited in a complex aglycon, the order of the reaction with respect to hydroxide ion concentration is no longer a function of the hydroxide ion concentration and in fact is quite similar to the reaction order observed with a simple aglycon (methoxy). The similarity (Table XIII) suggests that the nonunity values observed are a reflection of a change in the activity coefficient of the hydroxide ion as a function of the hydroxide ion concentration and temperature.

The pseudo-first-order rate constant can be related to the hydroxide concentration by the following expression [see Equation (3)],

$$k_r = k\,[^-OH]^b. \qquad (32)$$

[18] See Effect of Hydroxide Ion Concentration at Constant Ionic Strength under cleavage of the oxygen-aglycon bond, p. 72.

TABLE XIII

KINETIC REACTION ORDER WITH RESPECT TO HYDROXIDE ION CONCENTRATION FOR ALKALINE DEGRADATION OF VARIOUS COMPOUNDS AT 170°C.

Compound	Reference	Reaction Order
Sodium methyl α-D-glucopyranosiduronate	23	0.88
Methyl α-D-glucopyranoside	23	0.69
Methyl β-D-glucopyranoside	20	0.74
1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol[a]		0.66[b]
1,5-Anhydrocellobiitol at 0.5N sodium hydroxide; 2.0F sodium p-toluenesulfonate[a]		0.69[c]

[a]This study.

[b]Based on appearance of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.

[c]Based on appearance of 1,5-anhydroglucitol (XLV).

The hydroxide ion concentration used in Equation (32) is a simple estimate of the activity of the hydroxide ion, a_{OH^-}, where

$$a_{OH^-} = \gamma_{OH^-} [^-OH] \tag{33}$$

where γ_{OH^-} = activity coefficient of the hydroxide ion. Thus, Equation (32) is more accurately written as

$$k_r = k(\gamma_{OH^-} [^-OH])^b \tag{34}$$

thus

$$\ln k_r = \ln k + b(\ln \gamma_{OH^-} + \ln [^-OH]). \tag{35}$$

If an empirical function for $\ln (\gamma_{OH^-})$ developed by Akerlof and Kegeles (43) over the temperature range of 0-70°C. can be extrapolated to 170°C., the change in activity coefficient with hydroxide ion concentration has only a small effect

on the order of the reaction. Thus, the nonunity reaction order observed is the result of some other factor(s). The most obvious choice is multiple mechanism in which one portion of the reaction is unaffected by the hydroxide ion concentration. Alternately, the extrapolation of Akerlof's data may not be valid and the variation of the activity coefficient as a function of hydroxide ion concentration is much larger than predicted. Scanning Table XIII it will be noted that except for sodium methyl α-D-glucopyranosiduronate (0.88) the values for the reaction order with respect to hydroxide ion concentration all fall in the vicinity of 0.70. Robins (23) proposed a base catalyzed S_N1 mechanism for the alkaline degradation of methyl α-D-glucopyranosiduronate, i.e., ionization of the C-2 hydroxyl was visualized as being necessary to help stabilize the C-1 carbonium ion. The evidence found in this study for an S_N1 mechanism functioning at C-4 in 1,5-anhydrocellobiitol would seem to raise some questions about the necessity of ionization of the C-2 hydroxyl for stabilization of a C-1 carbonium ion, which is inherently more stable than the C-4 carbonium ion. Since Robins (23) did not control the total ionic strength, it is possible that the "reaction order" attributed to hydroxide ion is in fact a salt effect which fortuitously falls near one (Table XIII).

Effect of Ionic Strength at Constant Hydroxide Ion Concentration

Increasing the ionic strength of the reaction medium would be expected to produce different effects on the S_N1 and S_N1cB mechanisms. As was previously mentioned, increasing ionic strength increases the rate of an S_N1 reaction and decreases the rate of an S_N1cB reaction. Hence, the observed 15.5% decrease in the rate of alkaline cleavage of the glycosyl-oxygen bond with increasing ionic strength (0.5 to 2.5F) would appear to be consistent with a reaction proceeding by an $S_N1cB(2)$ and/or an $S_N1cB(4)$ mechanism. However, since the

magnitude of the effect of increasing ionic strength on a given mechanism cannot be predicted, the extent to which the reaction is governed by an S_N1cB type mechanism cannot be rigorously demonstrated. Thus, the potential exists for some participation in the cleavage of the glycosyl-oxygen bond by an S_N1 mechanism.

An estimate of the magnitude of the effect of ionic strength on an S_N1 mechanism at C-1 can be derived from the effect of increasing ionic strength (0.5 to 2.5F) on the heterolysis of the oxygen-aglycon bond (64% increase in rate). It should be noted, however, that a C-1 carbonium ion is inherently more stable than a C-4 carbonium ion. Hence, the effect of increasing ionic strength would be expected to be lower for an S_N1 mechanism involving the C-1' carbonium ion than that observed for oxygen-aglycon bond cleavage (C-4 carbonium ion). Similarly, an $S_N1cB(2)$ mechanism may be approximated by the alkaline degradation of 1,6-anhydro-β-D-glucopyranose[19] which exhibits a 35% decrease in rate with increasing ionic strength (0.5 to 2.5F).

The applicability of the above is so uncertain that it can be used in only a very qualitative manner. However, based on the above discussion and the observed data, it would seem that an $S_N1cB(2)$ and/or $S_N1cB(4)$ mechanism(s) govern a major portion of the cleavage of the glycosyl-oxygen bond in 1,5-anhydrocellobiitol.

[19] The reaction mechanism for the alkaline degradation 1,6-anhydro-β-D-glucopyranose has not been clearly established. However, the 35% decrease in rate with increasing ionic strength (0.5 to 2.5F) strongly suggests an S_N1cB or S_N2 type mechanism.

Alkaline Degradation of 1,5-Anhydromaltitol

1,5-Anhydromaltitol (XLVI) [1,5-anhydro-4-O-(α-D-glucopyranosyl)-D-glucitol] is the α-linked analog of 1,5-anhydrocellobiitol and, hence, $S_N1cB(2)$ (M=C) and $S_N1cB(4)$ mechanisms are precluded as governing mechanisms for its alkaline degradation. Alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydromaltitol could take place by an $S_N1cB(6)$ mechanism similar to that proposed by Robins (23) for methyl α-D-glucopyranoside (Fig. 29), and S_N1 mechanism (Fig. 30), or an S_N2 mechanism. Since no 1,6-anhydro-β-D-glucopyranose was detected in the reaction mixture, the $S_N1cB(6)$ mechanism is not functioning. Sufficient data are not available to rigorously disprove the occurrence of an S_N2 mechanism. However, S_N2 mechanisms have not been observed in other high-temperature alkaline degradations of glycosidic linkages (23). In addition, the increase in the pseudo-first-order rate constant with increasing ionic strength (Table VII) is indicative of an S_N1 mechanism. Thus, it is tentatively concluded that alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydromaltitol proceeds by an S_N1 mechanism (Fig. 30).

The obvious comparison of glycosyl-oxygen bond cleavage in 1,5-anhydrocellobiitol and 1,5-anhydromaltitol with regard to the portion of the reaction in 1,5-anhydrocellobiitol that proceeds by an S_N1 mechanism is not as simple as might be expected. Such a comparison assumes an equivalency in the S_N1 mechanisms of the α- and β-anomer which may not be present due to steric factors and the anomeric effect (13). The dipole moments for the axial glycosidic oxygen of the α-anomer (1,5-anhydromaltitol, XLVI) and the ring oxygen are antiparallel whereas in the β-anomer (1,5-anhydrocellobiitol, XIX) these two moments are at approximately right angles to each other (13). Thus, a larger net dipole moment is formed in the β-anomer than in the α-anomer, and the β-anomer is destabilized relative to the α-anomer. Therefore, the ground state energy for the β-anomer

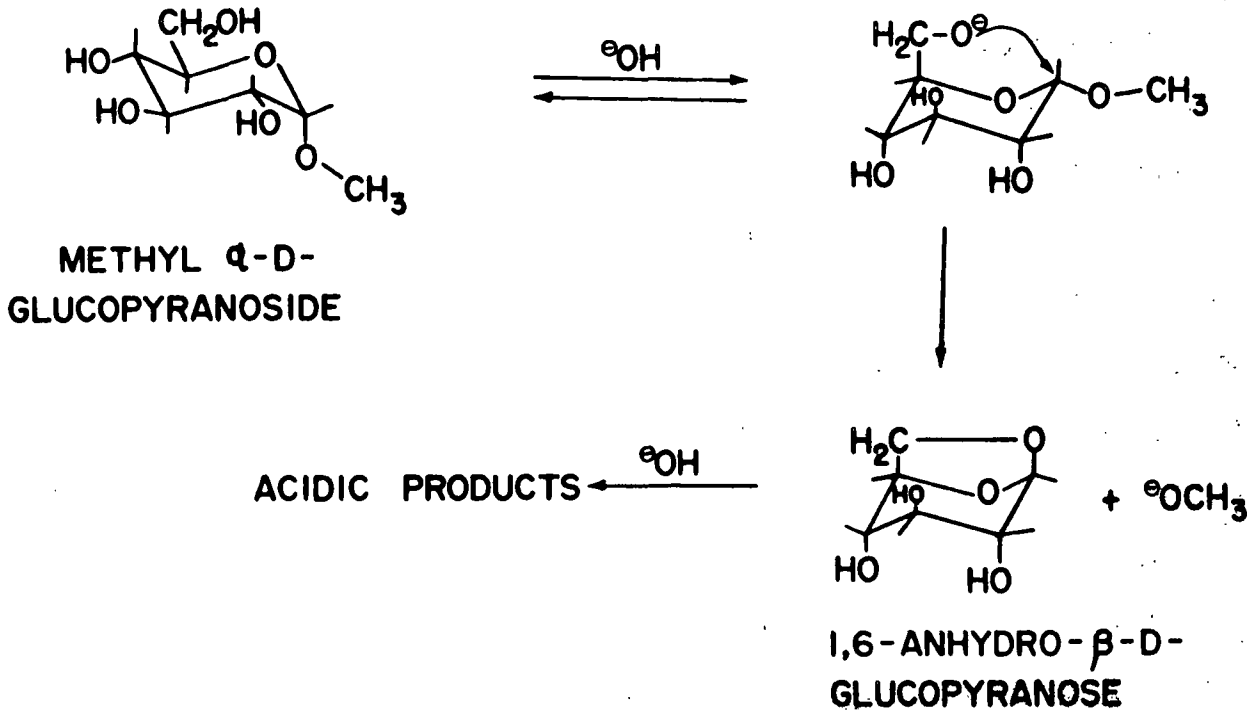


Figure 29. Proposed Mechanism for the Alkaline Degradation of Methyl α-D-Glucopyranoside (23)

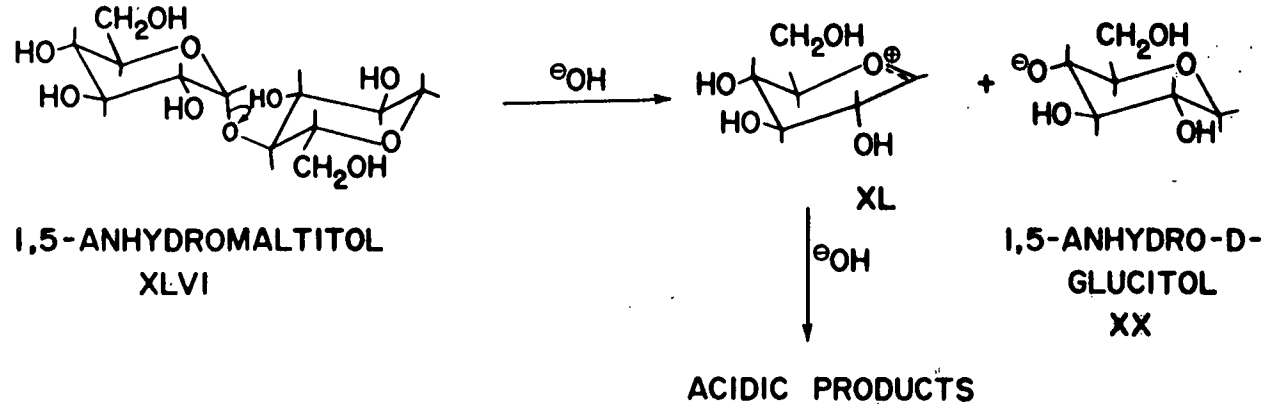
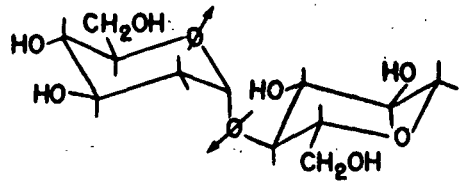
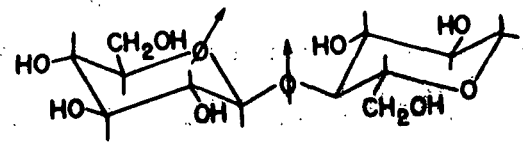


Figure 30. Potential Mechanism for the Alkaline Degradation of 1,5-Anhydromaltitol

is probably higher than that of the α-anomer and this should lower the free energy of activation (ΔF^*) for the β-anomer relative to the α-anomer, assuming the transition states are comparable, i.e., increase the rate of heterolysis of 1,5-anhydrocellobiitol relative to 1,5-anhydromaltitol.



1,5-Anhydromaltitol, XLVI



1,5-Anhydrocellobiitol, XIX

The rate constant for the alkaline cleavage of the glycosyl-oxygen bond in 1,5-anhydromaltitol is about 17% of the rate constant for the same bond cleavage in 1,5-anhydrocellobiitol (Tables II and VII). This indicates that the free energy of activation for the S_N1 mechanism in 1,5-anhydromaltitol is similar to the free energy of activation for the mechanism(s) governing glycosyl-oxygen bond cleavage in 1,5-anhydrocellobiitol. In addition, on the basis of the above discussion on the ground state energy of 1,5-anhydrocellobiitol, the free energy of activation for an S_N1 mechanism in 1,5-anhydrocellobiitol should be lower than in 1,5-anhydromaltitol. Hence, an S_N1 mechanism should be quite feasible in the alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol.

CONCLUSIONS REGARDING THE MECHANISM OF GLYCOSYL-OXYGEN BOND CLEAVAGE

The mechanism(s) involved in the alkaline cleavage of the glycosyl-oxygen bond cannot be specifically delineated with the data currently available. However, the data discussed above strongly imply a mixed mechanism (i.e., competition between two distinct mechanisms). In particular, the difference in the yield of 1,6-anhydro-β-D-glucopyranose from cleavage of the glycosyl-oxygen

bond of 1,5-anhydrocellobiitol and 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol suggests a mechanistic shift to an $S_N1cB(2)$ mechanism in the methylated disaccharide. Hence, a mixed mechanism is implied for the alkaline cleavage of 1,5-anhydrocellobiitol. The thermodynamic functions of activation also imply a mixed mechanism in that they are intermediate in value between the best available reference mechanisms [$S_N1cB(6)$ and S_N1]. The positive dependence on the hydroxide ion concentration exhibited by the rate of glycosyl-oxygen bond cleavage in conjunction with the negative dependence on ionic strength suggests a major portion of the reaction is governed by an S_N1cB type mechanism. In addition, comparable free energies of activation for the alkaline cleavage of the glycosyl-oxygen bonds in 1,5-anhydrocellobiitol and 1,5-anhydromaltitol (S_N1 mechanism) indicate that it is feasible for a significant portion of the cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol to proceed by an S_N1 mechanism.

Thus, all of the data for the alkaline cleavage of the glycosyl-oxygen bond of 1,5-anhydrocellobiitol are consistent with a mixed mechanism of which an S_N1 mechanism constitutes a significant portion. The remainder of the reaction is governed by S_N1cB mechanisms. Sufficient data are not available to differentiate between the $S_N1cB(2)$ and $S_N1cB(4)$ mechanism. However, on the basis of the proximity of the conjugate base, the $S_N1cB(2)$ mechanism would probably predominate.

CONCLUSIONS

Based on the observed results and theoretical considerations, it is concluded that 1,5-anhydrocellobiitol undergoes high temperature alkaline degradation in the absence of oxygen at both bonds of the glycosidic linkage.

It has been demonstrated that the degradation of 1,5-anhydrocellobiitol does not take place by a bimolecular nucleophilic substitution (S_N2) mechanism at either bond.

It is proposed that the oxygen-aglycon bond is cleaved exclusively by a unimolecular nucleophilic substitution (S_N1 mechanism; Fig. 21). The rate-determining step involves heterolysis of the bond between the glycosidic oxygen and C-4 of the 1,5-anhydro-D-glucitol moiety. The resultant 1,5-anhydro-4-deoxy-xylo-hexitol-4-cation subsequently yields 1,5:3,6-dianhydro-D-galactitol, trace amounts of 1,5-anhydro-D-gulitol, 1,5-anhydro-D-galactitol, and other products which were not identified but are presumed to be either ionic or small fragments.

Alkaline degradation of the glycosyl-oxygen bond does not appear to proceed by a single mechanism but rather exhibits characteristics which are consistent with a mixed mechanism involving both S_N1cB and S_N1 mechanisms. Delineation of the proportions of each of the above types of mechanisms is not feasible with the current data. However, the data do indicate the feasibility of an S_N1 mechanism governing a significant proportion of glycosyl-oxygen bond cleavage. While a distinction between an $S_N1cB(2)$ and an $S_N1cB(4)$ mechanism cannot be made on the basis of the available data, it seems most reasonable for the $S_N1cB(2)$ mechanism to predominate in glycosyl-oxygen bond cleavage.

CONSEQUENCES OF THE RESULTS OF THIS STUDY WITH REGARD TO THE ALKALINE DEGRADATION OF CELLULOSE

Historically the mechanism applied to the random cleavage of cellulose has been the $S_N1cB(2)$ mechanism. This mechanism, however, requires that the pyranose ring assume the 1C conformation prior to bond cleavage. In a long-chain polymer such as cellulose the "inertial" forces involved in rotating the substituents on C-1 and C-4 (glycosidic linkages) from the equatorial to the axial position should be considerably larger than those required in model compounds. In addition, the fact that the polymer chain is locked in a matrix (cellulose fiber) would further inhibit the change in conformation. This would seem to raise some fundamental questions as to the applicability of the $S_N1cB(2)$ mechanism to the alkaline cleavage of the cellulose polymer chain.

The proposed S_N1 mechanism does not require a change in pyranose ring conformation prior to bond cleavage. Since the S_N1 and S_N1cB mechanisms appear to be competitive in 1,5-anhydrocellobiitol, the feasibility of an S_N1 mechanism in the more restricted cellulose system would appear to be quite good. In fact, it may be that the S_N1 mechanism is the only viable mechanism for the alkaline cleavage of the cellulose chain.

Any attempt to extend the rate data gathered from homogeneous model compound systems to the alkaline cleavage of cellulose must be tempered by the realization that the heterogeneous nature of the cellulose system may alter both the rate due to any particular type of mechanism and the product distribution obtained.

EXPERIMENTAL

GENERAL ANALYTICAL PROCEDURES AND EQUIPMENT

Melting points were determined on a Thomas Hoover unimelt apparatus which had been calibrated against known compounds.

Elemental analyses were performed by Chemalytics, Inc. (2330 S. Industrial Park Dr., Tempe, Arizona).

NMR spectra were determined with a Varian A-60A spectrometer using either tetramethylsilane (TMS) as an internal standard in deuterochloroform or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard in D_2O. All spectra were determined at normal probe temperature.

IR spectra were determined on a Perkin-Elmer 621 grating infrared spectrophotometer.

Polarimetric measurements were made on either a Zeiss-Winkel visual polarimeter capable of being read to 0.01° or a Perkin-Elmer Model 141 MC recording polarimeter accurate to 0.01°.

TLC was conducted on microscope slides using silica gel G (Brinkman Instruments, Westbury, L.I., N.Y.). Spot visualization was accomplished by spraying the chromatograms with methanolic sulfuric acid (20%, vol.) and heating.

GLC was conducted on a Varian Aerograph Model 1200-1 gas chromatograph equipped with a hydrogen flame ionization detector. Recording and integration of the chromatographic response was with a Honeywell Electronic 16 recorder equipped with a Model 227 Disc chart integrator. Prepurified nitrogen (Matheson Gas Products) was used as the carrier gas. All columns were housed

in 1/8-in. O.D. stainless steel and rigged for on-column injection. The conditions used are listed below:

Conditions A: Column, 10% SE-30 on 60/80 mesh AW-DMCS Chromasorb W (3 ft.); nitrogen flow, 60 ml./min.; hydrogen pressure, 11.25 p.s.i.g.; column temp., 140-212°C. at 6°C. $min.^{-1}$, 212-310°C. at 15°C. $min.^{-1}$; injector temp., 275°C.; detector temp., 350°C.

Conditions B: Same as Conditions A except: column temp., 140-310°C. at 4°C. $min.^{-1}$.

Conditions C: Same as Conditions A except: column temp., 240-310°C. at 6°C. $min.^{-1}$.

Conditions D: Column, 10% SE-30 on 60/80 mesh AW-DMCS Chromasorb W (3 ft.); nitrogen flow, 20 ml./min.; hydrogen pressure, 8.25 p.s.i.g.; column temp., 130-230°C. at 6°C. $min.^{-1}$, 230-310°C. at 15°C. $min.^{-1}$; injector temp., 270°C.; detector temp., 350°C.

Conditions E: Column, 5% SE-30 on 60/80 mesh AW-DMCS Chromasorb W (10 ft.); nitrogen flow, 30 ml./min.; hydrogen pressure, 9 p.s.i.g.; column temp., 180°C.; injector temp., 250°C.; detector temp., 300°C.

Paper chromatography was conducted on Whatman No. 1 paper using ethyl acetate:pyridine:water (8:2:1, vol.) as the developer. The chromatograms were developed for approximately 38 hr. and visualized with alkaline silver nitrate reagents (44).

Mass spectra were determined on a DuPont Instruments Model 21-491 spectrometer interfaced via a jet separator with a Varian Aerograph Model 1440-1 gas chromatograph equipped with a hydrogen flame ionization detector. Recording of the gas chromatograph response and beam monitor response was with a Hewlett-Packard Model 7128A recorder. The mass spectra were recorded with a Century GPO 460 recorder.

Chromatographic separations on the Aerograph 1440 employed a 2 ft. x 1/8 inch stainless steel column (4.4% SE-30 on 60/80 mesh AW-DMCS Chromasorb G and the following conditions:

Helium (UHP Helium, minimum purity 99.999%; Matheson Gas Products, Joliet, Ill.) flow, 40 ml./min.; hydrogen flow, 10 ml./min.; column temp., 107°C.; injector temp., 250°C.; detector temp., 300°C.

The desired compounds were routed from the chromatograph to the mass spectrometer via a proportioning valve to the jet separator. The interfacing apparatus was maintained at the following temperatures: valve-interface block, 300°C.; connecting tube, 280°C.; jet separator, 250°C.

The mass spectrometer control settings were as follows:

Oven temp., 125°C.; source temp., 225°C.; sensitivity, 5.5; ionizing voltage, G.C. (70 volts) or V.I.V. (1.5-10 volts); scan, 40 sec./decade; chart speed, 1 inch/sec.; pressure during sample introduction, ca. 1 x 10^{-6} torr.

SYNTHESIS OF COMPOUNDS

1,5-ANHYDRO-D-GLUCITOL (XX)

Tetra-O-acetyl-α-D-glucopyranosyl bromide (XLVII) (45) was reduced with $LiAlH_4$ by the procedure of Ness, et al. (46) with the exception that tetrahydrofuran was substituted as the reaction solvent. Crystallization from absolute ethanol yielded XX (67.0%); m.p. 142-143°C., $[\alpha]_D^{24}$ + 42.8° (c 1.43, H_2O). Literature: m.p. 142-143°C., $[\alpha]_D^{20}$ + 42.8° (c 2.14, H_2O) (46).

HEPTA-O-ACETYL-α-CELLOBIOSYL BROMIDE (XLVIII)

α-Cellobiose octaacetate (20) (132 g.) was slurried in 1,2-dichloroethane (400 ml.) and reacted with hydrogen bromide in glacial acetic acid (30-32%, 135 ml.) for 1.0 hr. The reaction solution was diluted with chloroform (800 ml., A.R.), vigorously stirred with ice and water (2700 ml.) for 0.5 hr., washed with ice water (1 liter), aqueous sodium bicarbonate (1 liter), cold water (1 liter), dried ($CaCl_2$), and concentrated in vacuo to approximately 450 ml. The bromide,

XLVIII, crystallized on the addition of petroleum ether and refrigeration (105.3 g., 77.4%); m.p. 181.5-182.5°C. (decomp.). Literature: m.p. 180°C. (decomp.) (47).

1,5-ANHYDROCELLOBIITOL (XIX)

Hepta-O-acetyl-α-cellobiosyl bromide, XLVIII, (14 g.) 10% palladium on charcoal (500 mg.), trimethylamine (3 ml.), and absolute ethyl acetate (150 ml.) were placed in a modified Parr bomb and hydrogen applied at 40-50 p.s.i.g. for 12-24 hr. with stirring. The reduction was monitored by TLC (ethyl ether:pyridine, 20:1, vol.). Residual bromide, XLVIII, in the analytical sample was hydrolyzed with silver nitrate (3%) in aqueous acetone (19:1, vol.) prior to TLC. On completion, the reaction mixture was filtered, diluted with an equal amount of chloroform, and washed with saturated aqueous sodium bicarbonate (2 x 300 ml.) and water (300 ml.). Silver nitrate (3% in aqueous acetone, 5 ml.) was added, the solution shaken vigorously, dried ($CaCl_2$), filtered through Celite, and evaporated *in vacuo*. Two crystallizations from absolute ethanol yielded 1,5-anhydro-hepta-O-acetyl-cellobiitol (XLIX) (68.4%); m.p. 193.5-194.0°C., $[\alpha]_D^{24.5}$ + 4.1° (*c* 2.93, $CHCl_3$). Literature: m.p. 194°C., $[\alpha]_D^{25}$ + 4.6° (*c* 10, $CHCl_3$) (48).

XLIX was deacetylated with sodium methoxide in methanol (49). Two crystallizations from ethanol afforded XIX; m.p. 204.5-205.5°C., $[\alpha]_D^{24.5}$ + 28.2° (*c* 2.210, H_2O). Literature: m.p. 172°C., $[\alpha]_D^{25}$ + 29.5° (*c* 4.64, H_2O) (48); m.p. 204.5-205.5°C., $[\alpha]_D^{31}$ + 28.6° (*c* 2.716, H_2O) (29)[20].

[20]The specific optical rotation reported by McCloskey (29) is in error. The value reported above was calculated from McCloskey's original data.

n-BUTYL β-D-GLUCOPYRANOSIDE (L)

n-Butyl tetra-O-acetyl-β-D-glucopyranoside (50) was deacetylated with sodium methoxide in methanol (49). Three recrystallizations from ethyl acetate yielded L: m.p. 67-68°C., $[\alpha]_D^{20}$ - 36.7° (c 2.03, H_2O). Literature: m.p. 64-65°C., $[\alpha]_D$ - 34.1° (H_2O) (51).

CYCLOHEXYL β-CELLOBIOSIDE (LI)

Hepta-O-acetyl-α-cellobiosyl bromide, XLVIII, was reacted with cyclohexanol in a modified Koenigs-Knorr condensation using mercury salts as catalysts (50). Drierite (10-20 mesh, 40 g.), yellow mercuric oxide (13.5 g.), mercuric bromide (1 g.) and anhydrous cyclohexanol (60 ml.) were added to absolute chloroform (300 ml.) and stirred for 0.5 hr. to desiccate the system. XLVIII (44 g.) was added to the suspension and stirring was continued for approximately 8 hr. The suspension was filtered through Celite into 20% aqueous potassium iodide (300 ml.) and the Celite rinsed with chloroform. The chloroform layer was separated, washed with 20% aqueous potassium iodide (3 x 300 ml.), water, filtered through anhydrous calcium chloride, and concentrated in vacuo. Three crystallizations from absolute ethanol yielded cyclohexyl β-cellobioside heptaacetate (LII) (28 g., 62%); m.p. 202-203.5°C., $[\alpha]_D^{25}$ - 25.7°, $[\alpha]_{546.1}^{25}$ - 30.8° (c 3.9280, $CHCl_3$). (Found: C, 53.53; H, 6.48. $C_{32}H_{48}O_{18}$ requires C, 53.48; H, 6.45%.)

LII was deacetylated with sodium methoxide in methanol (49). Two crystallizations from absolute ethanol afforded LI: m.p. 206.5-207.5°C., $[\alpha]_D^{25}$ - 26.3°, $[\alpha]_{546.1}^{25}$ - 31.2° (c 2.66, H_2O). (Found: C, 51.15; H, 7.60. $C_{18}H_{32}O_{11}$ requires C, 50.94; H, 7.61%.) The β-configuration of the cyclohexoxy substituent of LI was confirmed by its NMR spectrum (D_2O) in which two doublets (H-1', δ 4.53, $J_{1',2'}$ = 6.9 Hz and H-1, δ 4.59, $J_{1,2}$ = 7.5 Hz), both characteristic of anomeric

protons associated with a β-glucopyranosidic bond, were evident (52). The indicated tentative assignments of anomeric proton resonances were made by comparison with the spectra (D_2O) of cyclohexyl β-D-glucopyranoside (H-1, δ 4.56, $J_{1,2}$ = 7.3 Hz) and 1,5-anhydrocellobiitol (H-1', δ 4.53, $J_{1',2'}$ = 7.0 Hz).

1,5-ANHYDROMALTITOL (XLVI)

Maltose octaacetate (17.9 g.) [m.p. 156-158°C.; literature m.p. 159-160°C. (53)], prepared by acetylating commercial maltose monohydrate with pyridine-acetic anhydride (54), was dissolved in 1,2-dichloroethane (50 ml.) and reacted with hydrogen bromide in acetic acid (30-32%, 18 ml.) for 50 minutes. The solution was diluted with chloroform (100 ml.) washed with ice water (5 x 100 ml.), dried ($CaCl_2$), and concentrated in vacuo to a sirup (22 g.). The sirup, absolute ethyl acetate (150 ml.), triethylamine (5 ml.), and 10% palladium on carbon catalyst (1 g.) were immediately placed in a modified Parr bomb and hydrogenated (70 p.s.i.g.) for 72 hr. with stirring. The reaction mixture was filtered, and the filter cake was rinsed with ethyl acetate. The combined ethyl acetate solutions were washed with water (200 ml.), saturated sodium bicarbonate (2 x 200 ml.), water (2 x 200 ml.), dried over Drierite, and evaporated to dryness in vacuo. The crude 1,5-anhydro-hepta-O-acetyl-maltitol (LIII) was purified by multiple-pass, silica gel, column chromatography. Typically, crude LIII (2.7 g.) containing less than 1% contaminant (GLC, cond. C) was fractionated on a silica gel column (Fisher Grade 950, 250 g.; 25 x 1000 mm.) with benzene:ethyl acetate (1:1, vol.). Pure (GLC) LIII (0.8 g.) was obtained in the initial fractions. Succeeding fractions contained progressively more contaminant and were rechromatographed. Crystallization from methanol yielded LIII: m.p. 136-136.5°C., $[\alpha]_D^{26}$ + 81.5° (c 3.45, $CHCl_3$). Literature: m.p. 133-134°C., $[\alpha]_D$ + 82.0 ($CHCl_3$) (55).

1,5-Anhydromaltitol (XLVI) is noncrystalline and was prepared for a kinetic run by deacetylation of an appropriate amount of LIII with sodium methoxide in methanol (49). The methanol was removed under reduced pressure and the thick sirup employed as such in kinetic experiments.

2,3,6-TRI-O-METHYL-D-GLUCOPYRANOSE (LIV)

Dimethyl sulfate (120 ml.) was added over 1.5 hr. to a vigorously stirred slurry of Dow Methocel (USP, 100 cps. viscosity, 40 g.) and powdered sodium hydroxide (120 g.) in tetrahydrofuran (1 liter). The stirred mixture was held at room temperature for an additional 2.5 hr., refluxed gently for 5 hr., and then allowed to stand at room temperature overnight. Benzene (470 ml.) and water (300 ml.) were added to the stirred mixture which was then refluxed for 1.5 hr.

The mixture was neutralized with concentrated HCl, concentrated *in vacuo* until severe bumping occurred, diluted with an equal volume of ethanol, dispersed with a high-speed stirrer, concentrated *in vacuo* until severe bumping occurred (*ca.* 400 ml.), diluted with ethanol (200 ml.), dispersed, filtered, and the filter cake air dried. The filter cake (150 g.) contained both partially methylated cellulose and salts.

A portion of the dried filter cake (30 g.) was dissolved in hot 72% sulfuric acid (170 ml.) under a nitrogen atmosphere and after 2 hr. with stirring, diluted with hot water (2200 ml.). The solution was maintained under nitrogen at 60°C. overnight, refluxed 3 hr., cooled, neutralized (sodium carbonate), made acidic (concentrated HCl, 2 ml.), and concentrated to approximately one liter by distillation. Two such hydrolyzates, which at this point are essentially saturated with various salts, were combined, neutralized (sodium carbonate),

extracted with chloroform (2 x 400 ml.) to remove 2,3,4,6-tetra-O-methyl-D-glucopyranose, and then extracted with ethyl acetate in a 2-liter, liquid-liquid extractor for 48 hr. The ethyl acetate extract was concentrated *in vacuo* to a sirup. Crystallization from isopropyl ether (800 ml.) at room temperature afforded LIV: m.p. 108-110°C., $[\alpha]_D^{20.6}$ + 70.0° (c 8.16; H_2O). Literature: m.p. 121-123°C., $[\alpha]_D$ + 70.5° (H_2O) (56).

1,5-ANHYDRO-2,3,6-TRI-O-METHYL-D-GLUCITOL (XLV)

2,3,6-Tri-O-methyl-D-glucopyranose (LIV) (16 g.) was acetylated with pyridine-acetic anhydride (54) using a modified work-up in which all aqueous phases were extensively back-extracted with fresh chloroform. The combined chloroform extracts were dried ($CaCl_2$) and concentrated *in vacuo* to yield crude 1,4-di-O-acetyl-2,3,6-tri-O-methyl-D-glucopyranose (LV) (19.6 g.) which could not be induced to crystallize.

LV (9.8 g.) was dissolved in dichloroethane (25 ml.) and reacted with hydrogen bromide in glacial acetic acid (30-32%, 8 ml.) for 15 minutes. The reaction was diluted with chloroform (80 ml.), washed with ice water (3 x 100 ml.), dried ($CaCl_2$), and concentrated *in vacuo* to a sirup (10.9 g.). The sirup, absolute ethyl acetate (150 ml.), triethylamine (5 ml.), and 10% palladium on carbon catalyst (1 g.) were immediately placed in a modified Parr bomb and hydrogenated (70 p.s.i.g.) for 18 hr. with stirring[21]. The reaction mixture was filtered and the filter cake rinsed with ethyl acetate. The combined ethyl acetate solutions were washed with water (200 ml.), saturated sodium bicarbonate

[21]The hydrogenation was checked for completeness by TLC (chloroform:ethyl acetate, 2:1, vol.). Residual bromide in the sample was hydrolyzed with silver nitrate (3% in aqueous acetone, 1:19, vol.) prior to TLC analysis.

(200 ml.), water (200 ml.), dried over Drierite, and concentrated *in vacuo* to yield crude 1,5-anhydro-4-*O*-acetyl-2,3,6-tri-*O*-methyl-D-glucitol (LVI) as a sirup (3.7 g.). Additional LVI contaminated with 4-*O*-acetyl-2,3,6-tri-*O*-methyl-D-glucopyranose was recovered from the aqueous phases by exhaustive extraction with chloroform.

LVI was deacetylated with sodium methoxide in methanol (49) and purified on a silica gel column (Fisher Grade 950, 100 g.; 25 x 500 mm.) with chloroform:methanol (20:1, vol.) to give TLC clean XLV which could not be induced to crystallize. Vacuum distillation (*ca.* 0.05 mm. Hg; b.p. 78°C.) and subsequent crystallization from isopropyl ether afforded 1,5-anhydro-2,3,6-tri-*O*-methyl-D-glucitol (XLV) (2.2 g.); m.p. 32-32.5°C., $[\alpha]_D^{25}$ + 53.8°, $[\alpha]_{546.1}^{25}$ + 63.5° (*c* 2.43, H_2O). (Found: C, 52.51; H, 8.91. $C_9H_{18}O_5$ requires C, 52.41; H, 8.80%.) The NMR spectrum of XLV (D_2O) had three methyl singlets at δ 3.38, 3.48, and 3.60 p.p.m.

1,5-ANDHYDRO-2,3,6-TRI-*O*-METHYL-CELLOBIITOL (XXXVI)

1,5-Anhydro-2,3,6-tri-*O*-methyl-D-glucitol (XLV) (1.08 g.), powdered Drierite (10 g.), Ag_2O (2 g.), and absolute chloroform (45 ml.) were mixed at room temperature in a light-protected round-bottom flask (100 ml.) by mechanically rotating the flask at a 45° angle. After 0.5 hr., 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide XLVII (4 g.) and iodine (0.050 g.) were added to the mixture and mixing continued. Additional XLVII (4 g.) and Ag_2O (2 g.) were added at 20 and 44 hr. The condensation was monitored by GLC (Conditions B). Prior to GLC analysis, residual bromide, XLVII, in the analytical sample was hydrolyzed with silver nitrate (3%) in aqueous acetone (19:1, vol.) and the excess silver precipitated by addition of an aqueous acetone solution saturated with sodium chloride. Completeness of reaction was judged by the amount of

XLV left relative to the amount of XXXVI formed. After 54 hr., the reaction was filtered and the residue rinsed with chloroform (100 ml.). The combined filtrates were washed with saturated $NaHCO_3$ (150 ml.), H_2O (100 ml.), dried ($CaCl_2$), evaporated *in vacuo* to a thick sirup, and acetylated with pyridine-acetic anhydride (54). The acetylated mixture was fractionated on a silica gel column (Fisher Grade 950, 275 g.; 25 x 1000 mm.) with chloroform:ethyl acetate (2:1, vol.). After most of the monosaccharides had been eluted (fractions monitored by GLC, Conditions B), the column was eluted with acetone to yield a crude disaccharide fraction (2.4 g.). The disaccharide fraction which was still contaminated with monosaccharides was deacetylated with sodium methoxide in methanol (49). Fractionation of the mixture on a silica gel column (Fisher Grade 950, 100 g.; 25 x 500 mm.) with chloroform:methanol (7:1, vol.) yielded TLC pure XXXVI (0.61 g.; 31.6%), which was eluted rapidly and preceded the α-linked disaccharide. XXXVI could not be induced to crystallize, and was isolated as an amorphous solid by drying *in vacuo*; $[\alpha]_D^{25}$ + 15.3° (*c* 1.90, H_2O). (Found: C, 48.89; H, 7.59. $C_{15}H_{28}O_{10}$ required C, 48.91; H, 7.66%.) Acid hydrolysis of XXXVI yielded two products, 1,5-anhydro-2,3,6-tri-*O*-methyl-D-glucitol and α,β-D-glucopyranose, which were determined by GLC analysis of the trimethylsilyl ether derivatives (Conditions D).

The β-configuration of XXXVI was demonstrated by its NMR spectrum (D_2O) in which a doublet (H-1', δ 4.45, $J_{1,2}$ = 7.0 Hz), characteristic of an anomeric proton associated with a β-glucopyranosidic bond, appeared (52). The NMR spectrum also contained three methyl singlets at δ 3.40, 3.52, and 3.63 p.p.m.

Acetylation of XXXVI with acetic anhydride-pyridine (54) and two crystallizations from methanol yielded 1,5-anhydro-2',3',4',6'-tetra-*O*-2,3,6-tri-*O*-methyl-cellobiitol: m.p. 80-80.5°C., $[\alpha]_D^{23.5}$ +

15.7°, $[\alpha]_{546}^{23.5}$ + 18.6° (c 3.38, $CHCl_3$). (Found: C, 51.34; H, 6.78. $C_{23}H_{36}O_{14}$ requires C, 51.49; H, 6.76%.)

1,5-ANHYDRO-D-GALACTITOL (XXIII)

Tetra-O-acetyl-α-D-galactopyranosyl bromide (LVII) (11.8 g.) (57), absolute ethyl acetate (150 ml.), 10% palladium on charcoal (1 g.), and triethylamine (4 ml.) were placed in a modified Parr bomb and hydrogenated at 40 p.s.i.g. The reduction was monitored by a TLC procedure in which residual bromine LVII in the analytical sample was hydrolyzed with silver nitrate (3%) in aqueous acetone (1:19, vol.) prior to analysis (isopropyl ether:pyrindine, 10:1, vol.). On completion, the reaction was filtered, diluted with an equal amount of chloroform, washed with saturated sodium bicarbonate (2 x 300 ml.), water (300 ml.), silver nitrate solution (3% in aqueous actone, 5 ml.) added, dried ($CaCl_2$), filtered through Celite, and concentrated in vacuo. Crystallization from absolute ethanol (30 ml.) yielded 1,5-anhydro-D-galactitol tetraacetate (LVIII) (51%): m.p. 73-74°C., $[\alpha]_D^{25}$ + 47.6° (c 2.24, $CHCl_3$). Literature: m.p. 75-76°C., $[\alpha]_D^{20}$ + 49.1 (c 0.82, $CHCl_3$) (58); m.p. 103-104°C., $[\alpha]_D^{20}$ + 47.9 (c 1.0, $CHCl_3$) (59).

LVIII was deacetylated with sodium methoxide in methanol (49). Crystallization from absolute ethanol afforded XXIII: m.p. 112-113°C., $[\alpha]_D^{24.5}$ + 76.5° (c 2.26, H_2O). Literature: 113-114°C., $[\alpha]_D^{20}$ + 76.6° (c 1.08, H_2O) (58).

1,5-ANHYDRO-D-GULITOL (XXII)

1,5-Anhydro-D-galactitol tetraacetate (LVIII) (0.49 g.) was reacted with liquid hydrogen fluoride (59) to produce a mixture of 1,5-anhydro-D-galactitol and 1,5-anhydro-D-gulitol. The product mixture was refluxed with 0.5N NaOH

overnight, deionized, and used without further purification as a standard for paper chromatographic and GLC analysis.

1,5:3,6-DIANHYDRO-D-GALACTITOL (XXI)

1,5-Anhydro-2,3,4-tri-O-benzoyl-6-O-(p-toluene sulfonyl)-D-galactitol was reacted with sodium methoxide in methanol to produce 1,5:3,6-dianhydro-D-galactitol (60). Two crystallizations from ethyl acetate afforded XXI: m.p. 143-145°C., $[\alpha]_D^{25}$ + 40.0° (c 2.01, H_2O). Literature: m.p. 145-146°C., $[\alpha]_D^{20}$ + 40.2 (c 2.054, H_2O) (60).

A sample of XXI (90 mg.) was acetylated with pyridine-acetic anhydride (54) for NMR analysis.

SODIUM p-TOLUENESULFONATE

Commercial sodium p-toluenesulfonate was crystallized from ethanol containing 10-20% water to yield large platelets which contained less than 0.1% water (Karl Fischer Method).

SODIUM IODIDE

Reagent-grade sodium iodide (Matheson, Coleman, and Bell, Cincinnati, Ohio) was dried at 105°C. overnight and stored over sodium hydroxide.

WATER

Water used in the analytical procedures was deionized and triply distilled (61). The triply-distilled water used to prepare solutions for kinetic experiments was also boiled for 0.5 hr., allowed to cool with a prepurified nitrogen purge, and sealed under nitrogen to insure that no CO_2 or O_2 was present.

KINETIC ANALYSIS

PREPARATION OF SOLUTIONS

A stock solution of sodium hydroxide (2 liters; 2.4953N; ρ = 1.0977 g./ml.) was prepared in a nitrogen atmosphere from Harlico sodium hydroxide concentrate and boiled, triply-distilled water and stored under nitrogen in a paraffin-lined, rubber-stoppered bottle. The nitrogen atmosphere was provided by a glove bag in which the air had been replaced by prepurified nitrogen (Matheson Gas Products Inc.) using a deflation-inflation cycle, which was repeated four times. The glove bag was then maintained at a slightly positive pressure with nitrogen to insure the exclusion of oxygen.

The more dilute sodium hydroxide solutions were prepared in a nitrogen environment by diluting an aliquot of the stock sodium hydroxide solution with boiled, triply-distilled water in a volumetric flask containing, when necessary, the appropriate amount of dry sodium p-toluenesulfonate or sodium iodide[22].

PREPARATION AND LOADING OF THE REACTOR

Oxygen was desorbed from the surface of the clean, dry reactor by prolonged (24-48 hr.) heating under vacuum (ca. 0.05 mm. Hg, 6-inch desiccator at 105-110°C.) followed by cooling under vacuum and removal from the desiccator in a nitrogen atmosphere. The reactant (amounts sufficient for 0.01M) and sodium hydroxide solution (100.0 ml., determined gravimetrically) were placed in the reactor and stirred magnetically to insure complete solution of the reactant. The assembled reactor was sealed, removed from the glove bag, and

[22]Sodium iodide was weighed into the volumetric flask in a dry box due to its severe hydroscopicity.

connected to the sampling system. The sampling system and constant temperature apparatus are described in Appendix I.

SAMPLING

After the reactor had come to temperature, the connecting lines and valves were purged by drawing two samples which were discarded. At the desired sampling times, the system was purged (one sample) and the desired number of samples were drawn into tared, 4 ml., screw-top vials. The precise amount of sample taken and internal standards[23] added were determined gravimetrically.

The samples (containing internal standard) were deionized by passage over an Amberlite MB-3 resin column (H^+, OH^-) (6-8 ml., 15 x 150 mm.) and eluted with triply-distilled water (16 ml.). If at this point the solution was deionized (i.e., pH ca. 6) an additional water elution (4 ml.) was used to insure that the sample was completely recovered from the column. If, however, the sample was not completely deionized (generally this occurred when large amounts of sodium p-toluenesulfonate were present initially) the diluted sample was passed over the same resin column a second time and the residual sample eluted from the resin column with triply-distilled water (8 ml.).

The eluent was concentrated to small volume (ca. 1 ml.) in vacuo in a pear-shaped flask (50 ml.), passed over a MB-3 resin column (2 ml., 15 x 150 mm.)[24] eluted with triply-distilled water (6 ml.), concentrated to a small volume in vacuo, transferred to an Erlenmeyer flask (10 ml., GGS) and concentrated to dryness in vacuo.

[23] Internal standards used were aqueous solutions of n-butyl β-D-glucopyranoside (ca. 3 x 10^{-3}M) and cyclohexyl β-cellobioside (ca. 7 x 10^{-3}M).

[24] This procedure removes some resin-related material which appears in the general disaccharide region in the GLC chromatogram.

GLC ANALYSIS

O-Acetyl Derivatives

The dried samples were acetylated with a mixture of pyridine (0.75 ml.) and acetic anhydride (0.25 ml.) with mechanical shaking. After 18 hr., crushed, distilled-water ice (8 ml.) was added to the acetylation mixture and the mixture was shaken mechanically for 0.5 hr. The aqueous mixture was extracted with chloroform (2 x 5 ml.) and the combined chloroform extracts were washed with 1N hydrochloric acid (2 x 10 ml.), water (10 ml.), saturated sodium bicarbonate (2 x 10 ml.), water (2 x 10 ml.), dried (sodium sulfate), and concentrated to dryness in vacuo. The acetylated sample was dissolved in chloroform (ca. 0.2 ml.) and analyzed by GLC (Conditions A).

When the original reactants were partially methylated, the water solubility of the partially methylated-partially acetylated materials was such that a modified procedure for working up the acetylation was required. The aqueous mixture of the acetates obtained initially in the acetylation work-up was extracted with chloroform (4 x 5 ml.) and the combined chloroform extracts were washed with 2N hydrochloric acid saturated with sodium chloride (10 ml.), saturated sodium bicarbonate to which sodium chloride (10% wt.) had been added (10 ml.) and water (2 x 10 ml.). The aqueous phase at each stage was back-extracted with chloroform (5 ml.) and the chloroform phases were combined for the succeeding stage. The final chloroform solution was treated as above and analyzed by GLC (Conditions D).

O-Trimethylsilyl Derivatives (TMS)

The dried samples were reacted with Tri Sil (1 ml.) at room temperature for 30 minutes and excess pyridine and silylating agent were removed in vacuo

at 30-35°C. Toluene (ca. 1 ml.) was added several times to aid in removing residual pyridine. Hexane (ca. 1 ml.) was added once to aid in removing residual toluene. The sample was dissolved in hexane (ca. 0.2 ml.) and analyzed by GLC (Conditions E).

PRODUCT ANALYSIS

1,5-ANHYDRO-D-GLUCITOL

The major neutral product from the alkaline degradation of 1,5-anhydrocellobiitol had a GLC retention time (Conditions A, acetate derivative; Conditions E, TMS derivative) and a paper chromatographic R_f identical to that of an authentic sample of 1,5-anhydro-D-glucitol.

1,5-Anhydro-D-glucitol was subjected to 2.5N sodium hydroxide at 170°C. for 168 hr. Analysis of the reaction mixture by GLC (Conditions A, acetate derivative) indicated 99.2% of the alditol remained. Similarly, 98.3% of the alditol remained after 471 hr. in 0.5N sodium hydroxide, 2.0F sodium p-toluenesulfonate at 170°C. GLC analysis (Conditions E, TMS derivatives) of the 1,5-anhydro-D-glucitol subjected to these conditions could not detect the presence of other 1,5-anhydro-D-alditols.

1,5:3,6-DIANHYDRO-D-GALACTITOL (XXI)

A large-scale reaction of 1,5-anhydrocellobiitol (ca. 8 g.) in 2.5N sodium hydroxide at 170°C. was carried out using the procedures described previously. After 71.5 hr., the reactor was cooled and the reaction mixture was deionized by passage over Amberlite IR-120 cationic ion exchange resin (150 ml., 25 x 100 cm.) and Amberlite MB-3 mixed bed resin (50 ml., 4.5 x 20 cm.). The neutral products were eluted from the resin column with distilled water (800

ml.) and the eluent was concentrated, *in vacuo*, to a sirup (5.1 g.) which was acetylated with pyridine-acetic anhydride (54).

The acetylated mixture was fractionated into mono- and disaccharide components on a silica gel column (Fisher Grade 950, 275 g., 25 x 1000 mm.) with chloroform:ethyl acetate (2:1, vol.). The trailing monosaccharide fractions which contained 1,5:3,6-dianhydro-D-galactitol (XXI) as well as other monosaccharides and a trace of disaccharide, was deacetylated with sodium methoxide in methanol (49). Fractionation of the deacetylated mixture on a silica gel column (Fisher Grade 950, 35 g., 12 x 500 mm.) with chloroform:methanol (5:1, vol.) yielded TLC pure XXI (50 mg.).

The TMS derivative of XXI was prepared as described previously and analyzed by GLC-mass spectrometry. A parent ion at 290 m/e, which is consistent with 1,5:3,6-dianhydro-D-galactitol, was verified by varying the ionizing voltages applied (see Appendix III).

The NMR spectra of XXI isolated from the reaction mixture and its peracetate were identical to the NMR spectra of authentic samples of 1,5:3,6-dianhydro-D-galactitol and its diacetate. The IR spectrum of XXI (sirup) and the IR spectrum of an authentic sample of 1,5:3,6-dianhydro-D-galactitol (as a sirup) were also virtually identical.

1,5-ANHYDRO-D-GULITOL

Normal GLC analysis (Conditions E, TMS derivatives) of reaction products indicated a compound with a retention time identical to that of an authentic sample of 1,5-anhydro-D-gulitol. In addition, certain fractions obtained during the isolation of 1,5:3,6-dianhydro-D-galactitol from the reaction mixture

above showed (GLC, Conditions E, TMS) a marked enrichment in the compound thought to be 1,5-anhydro-D-gulitol. Paper chromatography also demonstrated the presence of a compound in these fractions with an R_f identical to that of an authentic sample of 1,5-anhydro-D-gulitol. About 0.5% 1,5-anhydro-D-gulitol is generated in the alkaline degradation of 1,5-anhydrocellobiitol in 2.5N sodium hydroxide at 170°C.; 0.7% is formed in 0.5N sodium hydroxide, 2.0F sodium p-toluenesulfonate.

1,5-ANHYDRO-D-GALACTITOL

1,5-Anhydro-D-galactitol could not be detected by normal GLC analysis (Conditions E, TMS derivatives) of reaction product mixtures. However, similar GLC analysis of certain fractions obtained during the isolation of 1,5:3,6-dianhydro-D-galactitol from the large-scale reaction product mixture contained a small amount of a compound with the same GLC retention time (Conditions E, TMS derivative) and paper chromatographic R_f as an authentic sample of 1,5-anhydro-D-galactitol. It is estimated that the 1,5-anhydro-D-galactitol present represents no more than 0.2% of the reaction products.

α-LINKED DISACCHARIDES

No α-linked disaccharides could be detected by NMR in the disaccharide component of the large-scale reaction mixture.

NOMENCLATURE

$\underline{A}$ = "frequency factor" (empirical correlation coefficient), $sec.^{-1}$

$\underline{a}$ = constant

AC = 1,5-anhydrocellobiitol

AG = 1,5-anhydro-D-glucitol

$\underline{a}_{OH}$ = activity of hydroxide ion

$\underline{b}$ = constant

$\underline{C}_{\underline{i}_o}$ = concentration of product $\underline{i}$ at $\underline{t}$ = 0, mole/liter

$\underline{C}_{\underline{i},\underline{t}}$ = concentration of product $\underline{i}$ in the reaction mixture at time $\underline{t}$, mole/liter

$\underline{C}_{\underline{r}_o}$ = concentration of reactant at $\underline{t}$ = 0, mole/liter

$\underline{C}_{\underline{r},\underline{t}}$ = concentration of reactant at time $\underline{t}$, mole/liter

DAG = 1,5:3,6-dianhydro-D-galactitol

e = base for Naperian logarithms, 2.7183

$\underline{E}_{expt}$ = Arrhenius activation energy, kcal./mole

$\Delta\underline{F}^*$ = free energy of activation, kcal./mole

$\underline{h}$ = Planck's constant, 6.25×10^{-27} erg. sec.

$\Delta\underline{H}^*$ = enthalpy of activation, kcal./mole

$\underline{IS}$ = internal standard, mole

k = Boltzmann's constant, 1.380×10^{-6} erg. $degree^{-1}$

$\underline{k}$ = specific rate constant, $sec.^{-1}$

$\underline{k}_{\underline{dL}}$ = pseudo-first-order rate constant for the alkaline degradation of 1,6-anhydro-β-D-glucopyranose, $sec.^{-1}$

$\underline{k}_{\underline{fL}}$ = pseudo-first-order rate constant for the formation of 1,6-anhydro-β-D-glucopyranose, $sec.^{-1}$

$\underline{k}_{\underline{i}}$ = pseudo-first-order specific rate constant for the formation of product $\underline{i}$, $sec.^{-1}$

$\underline{k}_{\underline{r}}$ = pseudo-first-order rate constant for the degradation of reactant, $sec.^{-1}$

$\underline{L}$ = concentration of 1,6-anhydro-β-D-glucopyranose at time $\underline{t}$, mole/liter

$\underline{L}_o$ = concentration of 1,6-anhydro-β-D-glucopyranose, mole/liter

OA = oxygen-aglycon bond

$[^-OH]$ = concentration of hydroxide ion, mole/liter

$\underline{R}$ = concentration of reactant at time $\underline{t}$, mole/liter

$\underline{R}$ = gas constant, 1.987 cal. degree^{-1} mole^{-1}

$\underline{RF}_{\underline{x}}$ = response factor for compound $\underline{X}$

$\underline{R}_o$ = concentration of reactant at $\underline{t}$ = 0, mole/liter

$\underline{RR}_{\underline{x}}$ = relative ratio, the peak area of $\underline{X}$ divided by peak area of internal standard

$\underline{S}$ = reaction sample, g.

$\Delta\underline{S}^*$ = entropy of activation cal. degree^{-1} mole^{-1}

S_N1 = unimolecular nucleophilic substitution

S_N2 = bimolecular nucleophilic substitution

$S_N1cB(2)$ = unimolecular nucleophilic substitution by the conjugate base of C-2' hydroxyl

$S_N1cB(4)$ = unimolecular nucleophilic substitution by the conjugate base of C-4' hydroxyl

$\underline{t}$ = time, sec.

$\underline{T}$ = temperature, °K

TMAC = 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol

TMAG = 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol

$\underline{T}_{\underline{r}}$ = retention time, min.

UI = unidentified products

$\underline{X}$ = compound $\underline{X}$, mole

$\underline{X}'$ = compound $\underline{X}$ in reaction mixture, mole/liter

$\underline{X}_{\underline{i},\infty}$ = $\underline{X}_{\underline{i},\underline{t}}$ at completion

$X_{i,t}$ = mole fraction of product i at time t

$Y_{L,\infty}$ = mole fraction of 1,6-anhydro-β-D-glucopyranose formed based on glycosyl-oxygen bond cleavage

ρ = density, g./ml.

γ_{OH^-} = activity coefficient of the hydroxide ion

I = Phenyl β-D-glucopyranoside

II = 1,2-Anhydro-α-D-glucopyranose

III = 1,6-Anhydro-β-D-glucopyranose

IV = D-Glucopyranose

V = Phenyl α-D-mannopyranoside

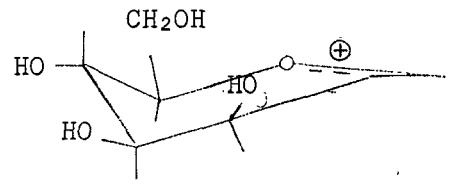
VI = 1,2-Anhydro-β-D-mannopyranose

VII = Phenyl β-D-xylopyranoside

VIII = 1,2-Anhydro-α-D-xylopyranose

IX = Phenyl β-D-mannopyranoside

X = D-Mannopyranosyl-cation



XI = 1,6-Anhydro-β-D-mannopyranose

XII = D-Mannopyranose

XIII = 1,4-Anhydro-α-D-mannopyranose

XIV = Phenyl α-D-galactopyranoside

XV = 1,6-Anhydro-β-D-galactopyranose

XVI = p-Nitrophenyl α-D-glucopyranose

XVII = 2-O-p-Nitrophenyl-D-glucopyranose

XVIII = 3-O-p-Nitrophenyl-D-glucopyranose

XIX = 1,5-Anhydrocellobiitol

XX = 1,5-Anhydro-D-glucitol

XXI = 1,5:3,6-Dianhydro-D-galactitol

XXII = 1,5-Anhydro-D-gulitol

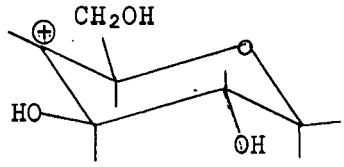
XXIII = 1,5-Anhydro-D-galactitol

XXIV = 1,5:3,4-Dianhydro-D-galactitol

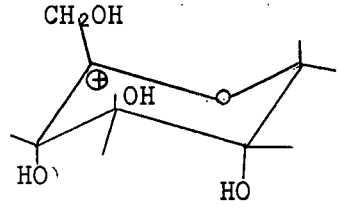
XXV = 1,5:2,3-Dianhydro-D-gulitol

XXVI = 1,5-Anhydro-D-iditol

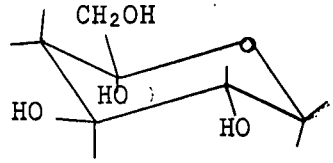
XXVII = 1,5-Anhydro-4-deoxy-D-xylo-hexitol-4-cation



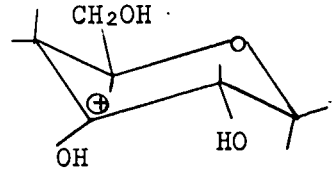
XXVIII = C-5 Carbonium ion



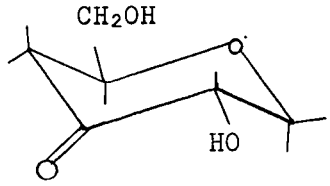
XXIX = 3-Deoxy-L-threo-2-hexulose



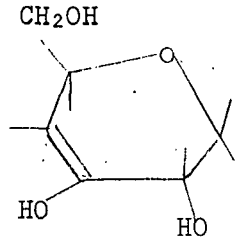
XXX = C-3 Carbonium ion



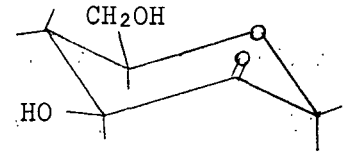
XXXI = 1,5-Anhydro-4-deoxy-D-erythro-3-hexulose



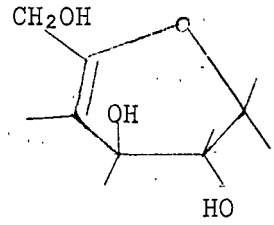
XXXII = 3,4-Enol



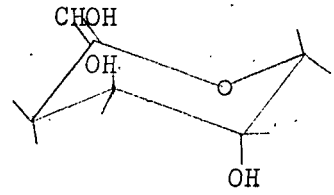
XXXIII = 1,5-Anhydro-4-deoxy-D-threo-2-hexulose



XXXIV = 4,5-Unsaturated sugar



XXXV = 5,6-Enol, aldo form 2,6 anhydro-3-deoxy-L-xylo-hexose



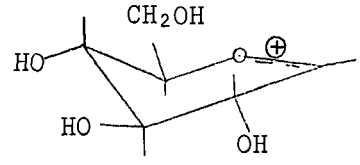
XXXVI = 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

XXXVII = 2,3-Anhydro-D-mannopyranose

XXXVIII = 3,4-Anhydro-D-altropyranose

XXXIX = 1,4-Anhydro-α-D-glucopyranose

XL = D-Glucopyranosyl-cation



XLI = D-Galactopyranose

XLII = 3,4-Anhydro-D-galactopyranose

XLIII = 3,6-Anhydro-D-galactopyranose

XLIV = 1,5-Anhydro-6-O-(α-D-glucopyranosyl)-D-glucitol; (1,5-anhydro-isomaltitol)

XLV = 1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol

XLVI = 1,5-Anhydromaltitol

XLVII = Tetra-O-acetyl-α-D-glucopyranosyl bromide

XLVIII = Hepta-O-acetyl-α-cellobiosyl bromide

XLIX = 1,5-Anhydro-hepta-O-acetyl-cellobiitol

L = n-Butyl β-D-glucopyranoside

LI = Cyclohexyl β-cellobioside

LII = Cyclohexyl hepta-O-acetyl-β-cellobioside

LIII = 1,5-Anhydro-hepta-O-acetyl-maltitol

LIV = 2,3,6-Tri-O-methyl-D-glucopyranose

LV = 1,4-Di-O-acetyl-2,3,6-tri-O-methyl-D-glucopyranose

LVI = 1,5-Anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-glucitol

LVII = Tetra-O-acetyl-α-D-galactopyranosyl bromide

LVIII = 1,5-Anhydro-tetra-O-acetyl-D-galactitol

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APPENDIX I

THE REACTION SYSTEM

The reactor, Fig. 31, was fabricated from Type 316 stainless steel with a total internal volume of 140 cc. The usable volume, however, was restricted to 100 cc. at room temperature to allow for thermal expansion at operating temperature. A positive pressure seal was provided by the teflon sealing ring which was compressed by the retaining bolts. The reactor has a design pressure limit of 500 p.s.i.g.

After assembly, the reactor was attached to a movable rack on the oil bath (316 stainless steel vessel, 15 x 7 x 12 inches) on which the valve for the sampling system was also mounted (Fig. 32). Lowering the rack positioned the reactor over a mechanically driven magnetic stirrer and approximately one inch under the surface of the heat transfer fluid (HTF = 100 ucon high temperature fluid; Matheson Scientific, 3.5 gal.).

The temperature of the oil bath was maintained by a Bronwell Constant Temperature Circulator (100-2000 watt heater, mercury contact thermoregulator rated at ±0.02°C.; Matheson Scientific). The temperature of the reaction mixture was monitored using an Inconel clad iron-constantan grounded thermocouple (Omega) in conjunction with a precision potentiometer (Cambridge Instrument Co., Ltd., London) (reads to 0.002 millivolt). The reference junction was an ice bath maintained at a constant temperature by the method of Braunstein and Ray (62). A continuous record of the temperature was provided by a Leeds and Northrup Speedomax W Model 101112 (1 millivolt range) recorder connected in parallel with the potentiometer. An adjustable, bucking-current circuit was used to bring the thermocouple output into the recorder's range (Fig. 33).

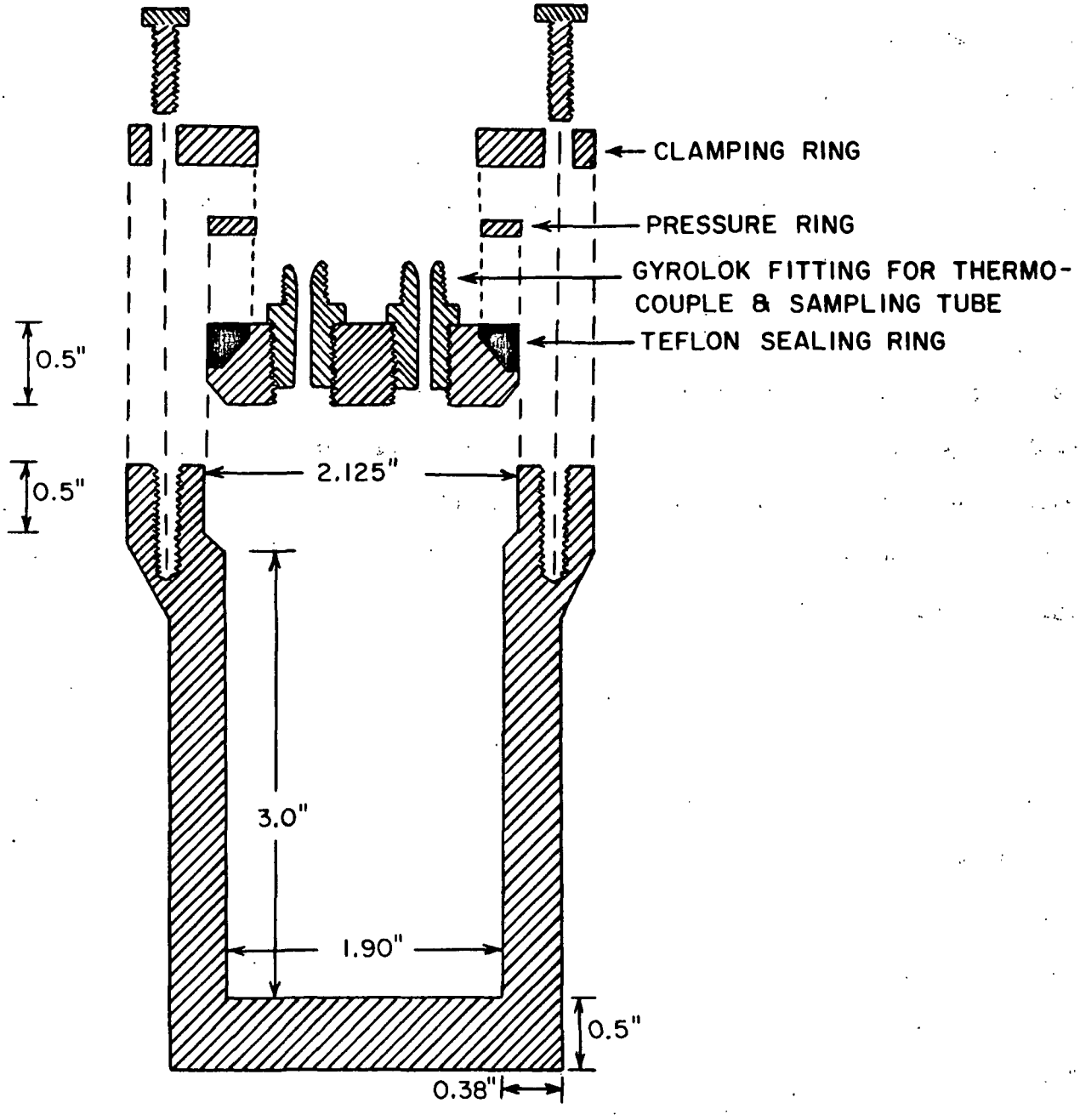

Figure 31. Reactor Fabricated for Kinetic Study of the Oxygen-Free Alkaline Degradation of 1,5-Anhydrocellobiitol

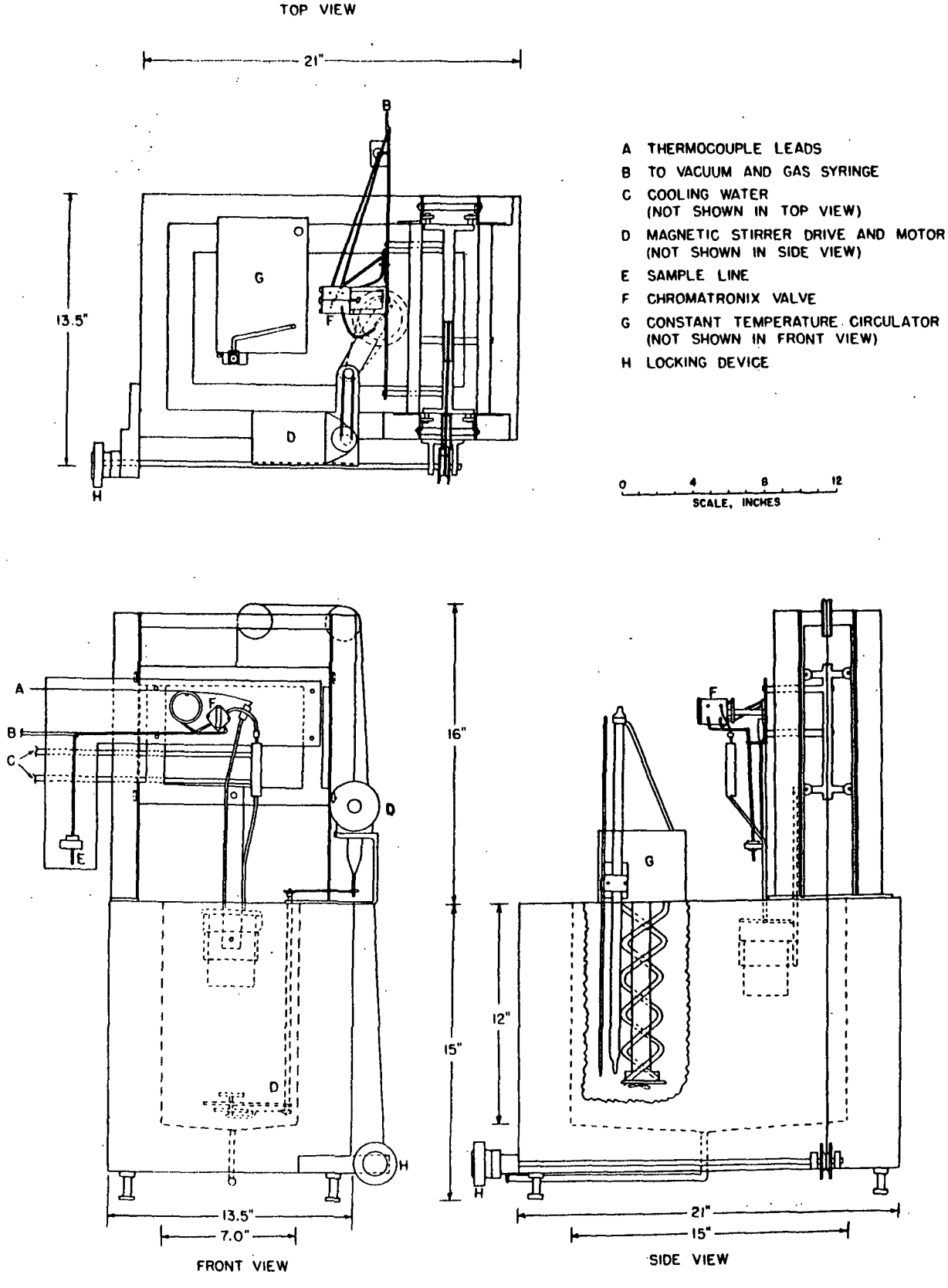

Figure 32. Temperature Controlling System

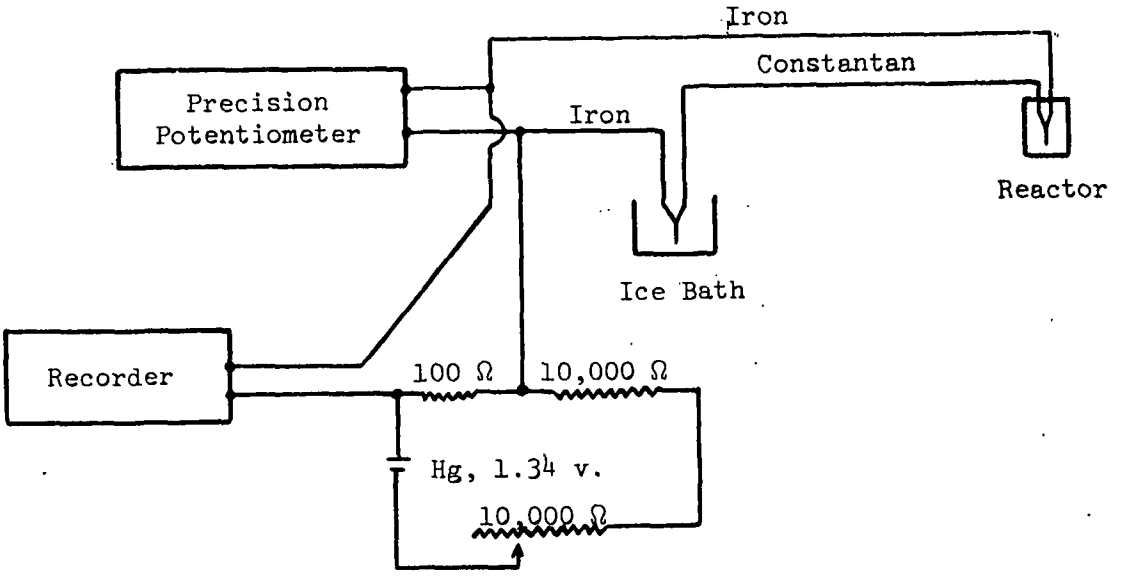

Figure 33. Schematic of Temperature Monitoring System

The sampling system (Fig. 34) consisted of a 1/8-inch Type 316 stainless steel capillary tube (sufficient clearance at the bottom of the reactor for the magnetic stirrer), which passed through a small heat exchanger (3 x 0.5 inches) before connecting with a Chromatronix eight-port, two-position, sampling valve (Chromatronix Inc., Berkeley, Calif.). The sample loop was connected so that in valve-position one the reactor was isolated and the gas syringe, sample loop, and the line to the sample vial were contiguous. In valve-position two the reactor and the sample loop were connected but isolated from the rest of the system. The sample loop (1.25 ml. capacity) was then filled until the pressure at the head of the loop was about equal to that in the reactor. When the valve was returned to position one, the sample (ca. 1.0 ml.) was pumped into the sample vial by applying a gentle positive pressure with the gas syringe. After the desired number of samples were taken, the sample loop was washed with water, ethanol, and then dried by applying a vacuum on the line from the gas syringe.

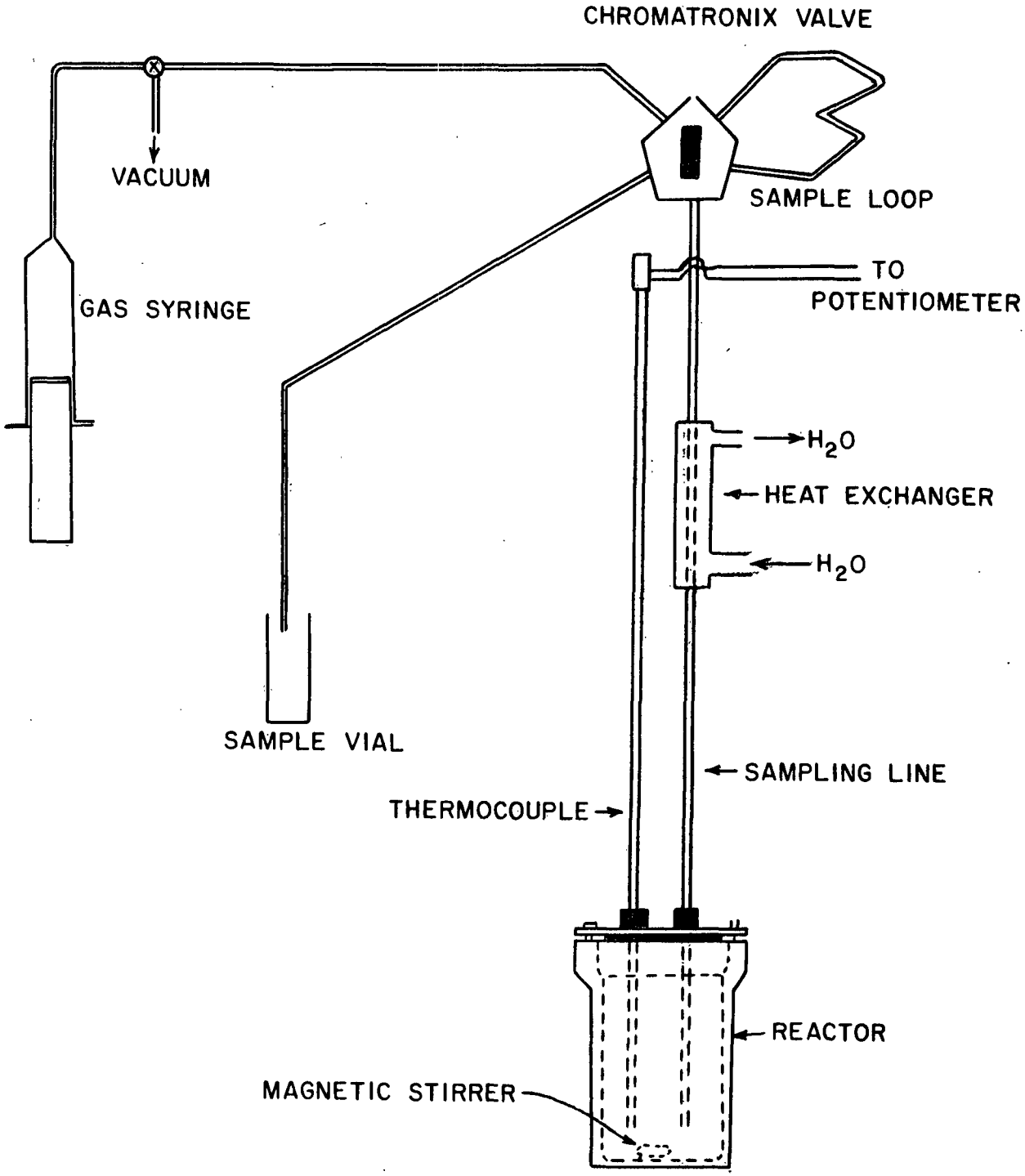

Figure 34. Schematic Representation of the Sampling System

A total of 30 ml. could be withdrawn from the reactor (100 ml. initial load) without changing the concentration of the nonvolatiles in solution by more than 0.18%.

APPENDIX II

GAS CHROMATOGRAPHIC RETENTION TIMES AND RESPONSE FACTORS OF SOME SELECTED MATERIALS

Response factors were calculated according to Equation (36)

$$(RF_X)(RR_X)(IS) = X \qquad (36)$$

where $\underline{RF}_{\underline{X}}$ = response factor for Compound $\underline{X}$,

$\underline{RR}_{\underline{X}}$ = relative ratio, the peak area of $\underline{X}$ divided by peak area of internal standard,

$\underline{IS}$ = internal standard, mole, and

$\underline{X}$ = Compound $\underline{X}$, mole.

The response factor was used to calculate the concentration of Compound $\underline{X}$ in the reaction mixture according to Equation (37).

$$10^{-3}(RF_X)(RR_X)(IS)\ \rho/S = X' \qquad (37)$$

where ρ = density of the reaction mixture, g./liter,

$\underline{S}$ = reaction sample, g., and

$\underline{X}'$ = Compound $\underline{X}$ in reaction mixture, mole/liter.

The gas chromatographic retention times and response factors of the compounds involved in the kinetic analysis of the alkaline degradation of 1,5-anhydrocellobiitol and 1,5-anhydromaltitol are shown in Table XIV.

The gas chromatographic retention times and response factors of the compounds involved in the analysis of the alkaline degradation of 1,5-anhydro-2,3,6-tri-$\underline{O}$-methyl-cellobiitol are shown in Table XV.

TABLE XIV

GAS CHROMATOGRAPHIC RETENTION TIMES AND RESPONSE FACTORS (CONDITION A) OF SOME SELECTED COMPOUNDS

Acetate of	T_r, min.	RF_x
1,5:3,6-Dianhydro-D-galactitol	2.6	2.583[a]
1,6-Anhydro-β-D-glucopyranose	4.5	1.788[a]
1,5-Anhydro-D-glucitol	6.4	1.408[a]
n-Butyl β-D-glucopyranoside	10.0	1.000[a]
1,5-Anhydromaltitol	16.0	1.316[b]
1,5-Anhydrocellobiitol	16.3	1.338[b]
Cyclohexyl β-cellobioside	18.5	1.000[b]

[a]Calculation based on n-butyl β-D-glucopyranoside.

[b]Calculation based on cyclohexyl β-cellobioside.

TABLE XV

GAS CHROMATOGRAPHIC RETENTION TIMES AND RESPONSE FACTORS (CONDITION D) OF SOME SELECTED COMPOUNDS

Acetate Derivative of	T_r, min.	RF_x
1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol	4.9	1.789[a]
1,6-Anhydro-β-D-glucopyranose	7.8	1.728[a]
n-Butyl β-D-glucopyranoside	13.7	1.000[a]
1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol	18.8	1.660[b]
Cyclohexyl β-cellobioside	23.9	1.000[b]

[a]Calculation based on n-butyl β-D-glucoside.

[b]Calculation based on cyclohexyl β-cellobioside.

The gas chromatographic retention times for some selected 1,5-anhydro-alditols are shown in Table XVI.

TABLE XVI

GAS CHROMATOGRAPHIC RETENTION TIMES (CONDITION E)
FOR SOME SELECTED COMPOUNDS

TMS Derivative of	T_r, min.
1,5-Anhydro-D-gulitol	16.5
1,5-Anhydro-D-galactitol	22.8
1,5-Anhydro-D-glucitol	29.1

APPENDIX III

GAS CHROMATOGRAPHIC-MASS SPECTROMETRIC ANALYSIS OF 1,5:3,6-DIANHYDRO-D-GALACTITOL

1,5:3,6-Dianhydro-D-galactitol was analyzed by mass spectrometry as the TMS derivative and the major peaks in the mass spectrum are listed in Table XVII. The base peak appears at an m/e of 117. The molecular ion at an m/e of 290 has an unusually high relative abundance as compared to the usual carbohydrate. This is probably due to the ether linkage involved in ring closure which eliminates the A fragmentation series and may affect the D, F, J, B, and E fragmentation series (63,64) since these routes should be facilitated by the glycosidic oxygen which is now missing.

TABLE XVII

MAJOR PEAKS IN MASS SPECTRUM OF THE TRI-METHYLSILYL DERIVATIVE OF 1,5:3,6-DIANHYDRO-D-GALACTITOL

m/e	Peak Height, mm.	Relative Abundance	m/e	Peak Height, mm.	Relative Abundance
290	27	73.0	145	7	18.9
275	8.5	23.0	143	8	21.6
257	2	5.4	131	15	40.5
245	1.5	4.1	129	28	75.7
231	1	2.7	117	37	100.0
217	11	29.7	116	24	64.7
204	29	78.5	110	5	13.5
199	4	10.8	103	15	40.5
191	16	43.2	101	17	46.0
185	9	24.3	89	3	8.1
171	16	43.2	81	5	13.5
169	5	13.5	75	29	78.4
157	23	62.2	74	16	43.2
147	11	29.7	73	32	86.5

The appearance of an M-15 peak (m/e 275) is characteristic of TMS derivatives (64). The peak at m/e 290 was demonstrated to be the molecular ion by varying the ionizing voltage. Since the molecular ion has the lowest appearance potential, lowering the ionization voltage should increase the molecular ion relative to the other peaks in the spectrum. Table XVIII shows the relative abundances obtained using the m/e 290 peak as the base peak. Several scans were made in the V.I.V. mode (variable ionizing voltage) at different voltages on one sample of 1,5:3,6-dianhydro-D-galactitol (TMS derivative) introduced into the mass spectrometer via g.l.c. The scans were run sequentially in the order listed (left to right). It can be seen by inspection that the relative abundance of the m/e 290 peak is enhanced by decreasing ionization voltage, hence, m/e 290 is the molecular ion. The noticeable difference in relative abundance at the same nominal ionization voltage is due to the varying concentration introduced into the mass spectrometer through g.l.c.

Analysis of the fragmentation pattern of 1,5:3,6-dianhydro-D-galactitol was not attempted.

TABLE XVIII

RELATIVE ABUNDANCE OF SELECTED PEAKS ON THE MASS SPECTRUM OF 1,5:3,6-DIANHYDRO-D-GALACTITOL BASED ON THE m/e 290 PEAK

		Relative Abundance, %					
m/e	V.I.V.	10.0	3.0	1.5	10.0	3.0	Volts
290		100	100	100	100	100	
275		26	19	21	13	11	
217		41	40	16	31	13	
204		235	149	106	123	97	
191		150	125	60	78	57	
157		197	136	84	142	75	
129		253	131	106	196	93	

APPENDIX IV

EXPERIMENTAL DATA

TABLE XIX

STABILITY OF 1,5-ANHYDROGLUCITOL (0.01M) IN 2.5678N SODIUM HYDROXIDE AT 170.0 ± 0.2°C.

Time, min.	1,5-Anhydroglucitol $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,5-Anhydroglucitol $\frac{\text{mole}}{\text{liter}} \times 10^3$
Initial		3991	10.162
samples in	10.261	7890	10.046
glove bag	10.213	7891	10.061
0	10.136	10080 Min.	10.222
1	10.240	sampled	10.051
2880	9.927	directly	10.156
2881	10.214	from cooled,	10.125
3990	10.186	open reactor	

TABLE XX

STABILITY OF 1,5-ANHYDROGLUCITOL (0.01M) IN 0.4961N SODIUM HYDROXIDE: 2.0F SODIUM p-TOLUENESULFONATE AT 169.8 ± 0.2°C.

Time, min.	1,5-Anhydroglucitol $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,5-Anhydroglucitol $\frac{\text{mole}}{\text{liter}} \times 10^3$
0	10.254	10367	10.105
1	10.366	10368	10.056
2303	10.178	26881	10.126
2304	10.129	26882	10.134

TABLE XXI

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.02M) IN 2.4746N SODIUM HYDROXIDE AT 170.2 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.000	0.043	0.164	18.969
1.0	0.000	0.036	0.160	19.145
2.1	0.000	0.041	0.172	19.174
37.0	0.023	0.106	0.443	18.834
99.3	0.070	0.202	0.949	18.203
100.0	0.071	0.215	0.951	18.295
186.0	0.138	0.288	1.650	17.273
301.7	0.223	0.335	2.502	16.276
303.2	0.236	0.334	2.511	16.331
502.4	0.358	0.277	3.862	14.766
702.1	0.507	0.271	5.039	13.351
703.1	0.515	0.256	5.019	13.510

$k_r = 8.44 \pm 0.12 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 7.22 \pm 0.08 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.76 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 2.21 \pm 0.25 \times 10^{-6}$, sec.$^{-1}$

TABLE XXII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL[a] (0.01M) IN 2.4953N SODIUM HYDROXIDE AT 169.8 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0	N.D.[b]	0.059	0.181	9.797
1	N.D.	0.067	0.179	9.785
30	N.D.	0.121	0.316	9.581
31	N.D.	0.068	0.313	9.700
180	N.D.	0.192	0.944	8.911
181	0.084	0.193	0.959	8.903
360	N.D.	0.222	1.615	8.074
361	N.D.	0.246	1.630	8.156
600	N.D.	0.201	2.317	7.352
601	0.249	0.199	2.336	7.358
900	N.D.	0.166	3.290	6.403
901	N.D.	0.185	3.396	6.374
1260	N.D.	0.154	4.085	5.366
1261	0.421	0.143	4.081	5.341

$\underline{k}_{\underline{r}} = 7.99 \pm 0.11 \times 10^{-6}$, sec.$^{-1}$

$\underline{k}_{\underline{AG}} = 7.23 \pm 0.08 \times 10^{-6}$, sec.$^{-1}$

$\underline{k}_{\underline{DAG}} = 0.81 \pm 0.03 \times 10^{-6}$, sec.$^{-1}$

$\underline{k}_{\underline{fL}} = 2.64 \pm 0.25 \times 10^{-6}$, sec.$^{-1}$

$\underline{k}_{\underline{OA}} = 0.64 \pm 0.12 \times 10^{-6}$, sec.$^{-1}$

---

[a] Run A.

[b] N.D. = not determined.

TABLE XXIII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL[a] (0.01M) IN 2.4953N SODIUM HYDROXIDE AT 169.8 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG mole/liter x 10^3	1,6-Anhydroglucose, L mole/liter x 10^3	1,5-Anhydroglucitol, AG mole/liter x 10^3	1,5-Anhydrocellobiitol, R mole/liter x 10^3
0.0	N.D.[b]	0.045	0.117	9.730
1.0	N.D.	0.042	0.120	9.701
2.0	N.D.	0.035	0.115	9.666
35.5	0.010	0.074	0.253	9.521
36.5	N.D.	0.084	0.258	9.578
106.5	0.044	0.130	0.546	9.155
107.5	N.D.	0.145	0.560	9.220
190.8	N.D.	0.173	0.898	8.863
192.2	N.D.	0.180	0.883	8.882
304.0	0.125	0.200	1.304	8.439
305.0	N.D.	0.202	1.309	8.365
492.5	N.D.	0.209	1.958	7.549
493.5	N.D.	0.215	1.972	7.599
723.7	0.276	0.190	2.688	6.882
724.7	N.D.	0.188	2.691	6.932

$k_r = 7.92 \pm 0.08 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 7.24 \pm 0.05 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.77 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 2.53 \pm 0.15 \times 10^{-6}$, sec.$^{-1}$

$k_{OA} = 0.71 \pm 0.12 \times 10^{-6}$, sec.$^{-1}$

---

[a] Run B.

[b] N.D. = not determined.

TABLE XXIV

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL[a] (0.01M) IN 2.4746N SODIUM HYDROXIDE AT 169.8 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG mole/liter x 10^3	1,6-Anhydroglucose, L mole/liter x 10^3	1,5-Anhydroglucitol, AG mole/liter x 10^3	1,5-Anhydrocellobiitol, R mole/liter x 10^3
0.0	0.008	0.037[b]	0.107	9.765
1.5	0.011	N.D.	0.109	9.822
2.6	0.009	0.023	0.157	9.853
36.3	0.023	0.082	0.265	9.588
94.1	0.049	0.141	0.503	9.490
95.2	0.044	0.133	0.513	9.456
184.0	0.088	0.181	0.877	8.978
311.6	0.145	0.206	1.366	8.459
312.7	0.131	0.212	1.382	8.587
481.1	0.200	0.228	1.999	7.959
722.5	0.293	0.193	2.781	7.013
723.7	0.302	0.202	2.814	6.985

$k_{-r} = 7.75 \pm 0.11 \times 10^{-6}$, sec.$^{-1}$

$k_{-AG} = 7.42 \pm 0.08 \times 10^{-6}$, sec.$^{-1}$

$k_{-DAG} = 0.79 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{-fL} = 2.52 \pm 0.05 \times 10^{-6}$, sec.$^{-1}$

$k_{-OA} = 0.31 \pm 0.15 \times 10^{-6}$, sec.$^{-1}$

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[a] Run C.

[b] N.D. = not determined.

TABLE XXV

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 1.4895N SODIUM HYDROXIDE; 1.0F SODIUM p-TOLUENESULFONATE AT 169.9 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.011	0.041	0.126	9.776
1.3	0.010	0.038	0.134	9.719
2.8	0.010	0.040	0.136	9.824
45.4	0.027	0.082	0.290	9.548
121.5	0.054	0.144	0.547	9.320
122.6	0.054	0.151	0.559	9.269
214.2	0.086	0.197	0.876	8.837
361.9	0.142	0.224	1.346	8.333
364.5	0.146	0.221	1.373	8.405
584.6	0.218	0.239	2.048	7.676
901.9	0.317	0.226	2.854	6.756
903.0	0.336	0.245	2.917	6.788

$k_r = 6.74 \pm 0.12 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 6.23 \pm 0.07 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.71 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 2.22 \pm 0.21 \times 10^{-6}$, sec.$^{-1}$

$k_{OA} = 0.53 \pm 0.11 \times 10^{-6}$, sec.$^{-1}$

TABLE XXVI

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.9925N SODIUM HYDROXIDE; 1.5-F SODIUM p-TOLUENESULFONATE AT 169.9 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	N.D.	0.076	9.515
1.1	0.0	N.D.	0.079	9.565
2.3	0.0	N.D.	0.076	9.659
48.8	N.D.[a]	N.D.	0.212	9.451
117.2	0.058	0.133	0.382	9.316
118.4	0.039	0.143	0.405	9.252
228.0	0.094	0.195	0.697	8.872
372.5	0.142	0.231	1.077	8.507
374.0	0.112	0.236	1.093	8.370
603.3	0.176	0.265	1.633	7.712
902.0	0.265	0.261	2.293	7.054
903.4	0.264	0.261	2.300	7.985

$k_r = 5.84 \pm 0.11 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 5.00 \pm 0.06 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.57 \pm 0.04 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 1.80 \pm 0.25 \times 10^{-6}$, sec.$^{-1}$

$k_{OA} = 0.82 \pm 0.11 \times 10^{-6}$, sec.$^{-1}$

[a] N.D. = not determined.

TABLE XXVII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.4974N SODIUM HYDROXIDE; 2.0F SODIUM p-TOLUENESULFONATE AT 169.8 ± 0.2°C.

Time, min.	1,5:3,6-Di-anhydrogalact-itol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydro-glucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-glucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-cellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	N.D.	0.080	9.852
1.2	0.0	N.D.	0.071	9.683
2.5	0.0	N.D.	0.072	9.635
66.0	N.D.[a]	0.072	0.195	9.425
164.2	0.045	0.118	0.376	9.231
165.5	0.034	0.125	0.386	9.140
306.8	0.053	0.199	0.656	8.807
511.4	0.093	0.222	1.029	8.401
512.4	0.103	0.234	1.036	8.500
803.4	0.168	0.324	1.541	7.800
1205.9	0.248	0.351	2.205	7.115
1207.6	0.233	0.325	2.176	6.967

$k_r = 4.38 \pm 0.11 \times 10^{-6}$, $sec.^{-1}$

$k_{AG} = 3.51 \pm 0.06 \times 10^{-6}$, $sec.^{-1}$

$k_{DAG} = 0.40 \pm 0.03 \times 10^{-6}$, $sec.^{-1}$

$k_{fL} = 1.12 \pm 0.19 \times 10^{-6}$, $sec.^{-1}$

$k_{OA} = 0.85 \pm 0.13 \times 10^{-6}$, $sec.^{-1}$

[a] N.D. = not determined.

TABLE XXVIII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.9979N SODIUM HYDROXIDE AT 170.1 ± 0.3°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.000	0.024	0.098	9.456
1.3	0.000	0.034	0.101	9.500
2.4	0.000	0.030	0.107	9.587
50.5	0.028	0.068	0.250	9.511
108.8	0.047	0.119	0.433	9.124
110.1	0.043	0.114	0.431	9.035
227.7	0.070	0.167	0.770	8.729
358.7	0.109	0.207	1.139	8.265
359.9	0.122	0.207	1.146	8.291
616.6	0.189	0.240	1.803	7.543
887.7	0.264	0.218	2.455	6.831
889.0	0.264	0.222	2.445	6.853

$k_r = 6.24 \pm 0.12 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 5.45 \pm 0.06 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.60 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 1.93 \pm 0.23 \times 10^{-6}$, sec.$^{-1}$

TABLE XXIX

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.5010N SODIUM HYDROXIDE AT 169.8 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.000	0.029	0.116	9.696
1.4	0.000	0.026	0.121	9.652
2.6	0.000	0.029	0.126	9.627
60.3	N.D.[a]	0.070	0.263	9.442
161.0	N.D.	0.131	0.492	9.089
162.3	N.D.	0.145	0.508	9.248
309.1	0.067	0.210	0.842	8.843
501.2	0.104	0.248	1.238	8.391
502.4	0.101	0.260	1.238	8.298
803.9	0.162	0.299	1.857	7.604
1206.2	0.229	0.298	2.592	6.880
1207.5	0.232	0.287	2.582	6.893

$k_r = 4.69 \pm 0.08 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 4.16 \pm 0.06 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.39 \pm 0.01 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 1.42 \pm 0.23 \times 10^{-6}$, sec.$^{-1}$

[a] N.D. = not determined.

TABLE XXX

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.4972N SODIUM HYDROXIDE; 2.0F SODIUM IODIDE AT 170.0 ± 0.02°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.00	0.007	0.052	9.896
1.2	0.00	0.009	0.060	9.878
2.3	0.00	0.010	0.059	9.874
64.6	0.015	0.045	0.174	9.599
162.3	0.032	0.082	0.357	9.490
163.4	0.038	0.090	0.356	9.510
303.3	0.066	0.140	0.615	9.259
503.6	0.105	0.171	0.931	8.722
504.8	0.112	0.172	0.939	8.681
807.4	0.158	0.212	1.417	8.118
1203.3	0.243	0.223	1.987	7.471
1204.6	0.237	0.225	1.976	7.399

$k_r = 3.94 \pm 0.07 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 3.10 \pm 0.04 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.38 \pm 0.01 \times 10^{-6}$, sec.$^{-1}$

TABLE XXXI

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 2.4746N SODIUM HYDROXIDE AT 179.8 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.029	0.087	0.364	9.057
0.7	0.027	0.084	0.372	9.204
1.5	0.030	0.088	0.382	9.113
13.8	0.045	0.107	0.507	9.074
30.3	0.056	0.127	0.681	8.851
31.3	0.058	0.130	0.681	8.856
64.1	0.076	0.158	1.004	8.574
102.6	0.123	0.172	1.386	8.082
103.6	0.130	0.158	1.390	8.046
160.1	0.192	0.171	1.882	7.474
242.2	0.280	0.163	2.524	6.744
243.3	0.280	0.160	2.541	6.692

$k_r = 21.37 \pm 0.43 \times 10^{-6}$, $sec.^{-1}$

$k_{AG} = 19.01 \pm 0.25 \times 10^{-6}$, $sec.^{-1}$

$k_{DAG} = 2.19 \pm 0.13 \times 10^{-6}$, $sec.^{-1}$

TABLE XXXII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.5090N SODIUM HYDROXIDE; 2.0F SODIUM p-TOLUENESULFONATE AT 180.2 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	0.027	0.098	9.462
0.9	0.0	0.034	0.109	9.489
1.8	0.0	0.030	0.143	9.468
22.2	0.023	0.056	0.228	9.262
62.5	0.042	0.114	0.440	9.093
63.3	0.040	0.111	0.451	9.099
113.3	0.070	0.144	0.696	8.588
199.4	0.117	0.208	1.134	8.198
200.7	0.123	0.209	1.154	8.158
312.3	0.184	0.244	1.652	7.684
453.9	0.265	0.254	2.259	6.920
454.8	0.269	0.261	2.282	6.872

$k_r = 11.64 \pm 0.22 \times 10^{-6}$, $sec.^{-1}$

$k_{AG} = 9.75 \pm 0.14 \times 10^{-6}$, $sec.^{-1}$

$k_{DAG} = 1.19 \pm 0.04 \times 10^{-6}$, $sec.^{-1}$

TABLE XXXIII

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 2.4953N SODIUM HYDROXIDE AT 160.3 ± 0.3°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	0.014	0.052	9.361
1.2	0.0	0.015	0.055	9.410
2.2	0.0	0.013	0.054	9.475
83.6	0.008	0.045	0.176	9.321
206.4	0.027	0.082	0.372	9.041
207.4	0.026	0.077	0.361	9.014
392.1	0.036	0.113	0.649	8.743
638.7	0.085	0.137	1.109	8.289
639.7	0.076	0.137	1.016	8.352
1068.6	0.152	0.146	1.597	7.699
1592.1	0.186	0.139	2.246	6.950
1593.0	0.204	0.139	2.237	6.910

$k_r = 3.21 \pm 0.04 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 2.84 \pm 0.05 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.26 \pm 0.01 \times 10^{-6}$, sec.$^{-1}$

TABLE XXXIV

DEGRADATION OF 1,5-ANHYDROCELLOBIITOL (0.01M) IN 0.4955N SODIUM HYDROXIDE; 2.0F SODIUM p-TOLUENESULFONATE AT 160.1 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,6-Anhydroglucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydrocellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	0.0	0.028	9.423
1.0	0.0	0.0	0.027	9.483
2.1	0.0	0.0	0.028	9.444
193.4	N.D.[a]	0.042	0.171	9.334
461.3	0.022	0.085	0.366	9.026
462.4	0.017	0.098	0.380	9.101
801.5	0.050	0.137	0.633	8.865
1295.6	0.080	0.174	0.976	8.353
1296.8	0.077	0.177	0.979	8.371
2137.2	0.141	0.212	1.544	7.779
3223.1	0.202	0.217	2.215	7.007
3224.1	0.221	0.236	2.221	6.891

$k_{-r} = 1.59 \pm 0.03 \times 10^{-6}$, sec.$^{-1}$

$k_{-AG} = 1.39 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{-DAG} = 0.14 \pm 0.01 \times 10^{-6}$, sec.$^{-1}$

[a] N.D. = not determined.

TABLE XXXV

DEGRADATION OF 1,5-ANHYDROMALTITOL (0.01M) IN 1.4893N SODIUM HYDROXIDE; 1.0F SODIUM p-TOLUENESULFONATE AT 170.0 ± 0.3°C.

Time, min.	1,5:3,6-Di-anhydrogalact-itol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-glucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-maltitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
1.2	0.0	0.013	9.172
2.4	0.0	0.013	9.258
91.7	N.D.[a]	0.068	9.215
227.7	N.D.	0.140	9.054
424.4	N.D.	0.244	8.913
425.4	N.D.	0.245	8.980
739.7	0.026	0.418	8.793
740.8	0.028	0.412	8.874
1201.9	0.057	0.684	8.627
1804.8	0.085	0.973	8.155
1805.8	0.060	0.978	8.230
2870.9	0.120	1.542	7.614
2871.8	0.154	1.578	7.539
4470.6	0.288	2.267	6.752

$k_r = 1.16 \pm 0.03 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 1.05 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.13 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

[a] N.D. = not determined.

TABLE XXXVI

DEGRADATION OF 1,5-ANHYDROMALTITOL (0.01M) IN 1.5086N SODIUM HYDROXIDE AT 170.1 ± 0.2°C.

Time, min.	1,5:3,6-Dianhydrogalactitol, DAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydroglucitol, AG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydromaltitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.0	0.029	9.384
1.4	0.0	0.033	9.314
2.5	0.0	0.033	9.463
202.2	N.D.[a]	0.147	9.271
719.5	0.028	0.463	8.920
720.5	0.029	0.465	9.079
1302.5	0.060	0.740	8.489
2109.3	0.117	1.143	8.138
2110.5	0.107	1.140	8.137
3017.2	0.191	1.159	7.625
4394.9	0.267	2.180	7.123
4395.9	0.283	2.245	7.055

$k_r = 1.08 \pm 0.03 \times 10^{-6}$, sec.$^{-1}$

$k_{AG} = 1.01 \pm 0.02 \times 10^{-6}$, sec.$^{-1}$

$k_{DAG} = 0.14 \pm 0.01 \times 10^{-6}$, sec.$^{-1}$

[a] N.D. = not determined.

TABLE XXXVII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.4953N SODIUM HYDROXIDE AT 170.1 ± 0.3°C.

Time, min.	1,6-Anhydro-glucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-glucitol, TMAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.070	0.158	10.772
1.2	0.072	0.173	11.053
2.6	0.082	0.178	11.342
37.7	0.174	0.360	11.071
98.3	0.283	0.633	10.704
99.6	0.296	0.619	10.174
176.8	0.379	0.963	10.184
266.5	0.423	1.397	9.782
268.1	0.428	1.341	9.788
403.0	0.466	1.818	8.744
595.1	0.455	2.404	8.382
596.1	0.444	2.522	8.079

$k_r = 8.49 \pm 0.42 \times 10^{-6}$, $sec.^{-1}$

$k_{TMAG} = 7.43 \pm 0.30 \times 10^{-6}$, $sec.^{-1}$

$k_{fL} = 5.40 \pm 0.25 \times 10^{-6}$, $sec.^{-1}$

TABLE XXXVIII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 1.4938N SODIUM HYDROXIDE; 1.0F SODIUM p-TOLUENESULFONATE AT 170.0 ± 0.2°C.

Time, min.	1,6-Anhydro-glucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-glucitol, TMAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.058	0.094	10.571
1.5	0.047	0.075	10.646
3.2	0.060	0.092	11.218
48.0	0.136	0.235	11.059
118.5	0.247	0.444	10.316
119.7	0.247	0.470	10.683
201.3	0.356	0.711	10.160
352.5	0.464	1.150	9.376
353.8	0.432	1.122	9.403
600.1	0.495	1.797	8.649
861.0	0.462	2.410	7.989
862.3	0.464	2.371	7.911

$k_r = 6.37 \pm 0.32 \times 10^{-6}$, sec.$^{-1}$

$k_{TMAG} = 4.85 \pm 0.14 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 4.13 \pm 0.45 \times 10^{-6}$, sec.$^{-1}$

TABLE XXXIX

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 0.4961N SODIUM HYDROXIDE; 2.0F SODIUM p-TOLUENESULFONATE AT 170.2 ± 0.2°C.

Time, min.	1,6-Anhydro-glucose, L $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-glucitol, TMAG $\frac{\text{mole}}{\text{liter}} \times 10^3$	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, R $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.0	0.048	0.084	9.980
1.3	0.054	0.084	9.972
2.8	0.059	0.107	10.004
60.9	0.108	0.198	10.180
154.5	0.187	0.336	9.820
156.3	0.196	0.361	9.832
273.0	0.278	0.534	9.338
501.2	0.389	0.875	8.965
502.4	0.391	0.872	9.082
742.9	0.463	1.208	8.843
1090.0	0.517	1.612	8.214
1091.3	0.504	1.593	8.140

$k_r = 3.10 \pm 0.14 \times 10^{-6}$, sec.$^{-1}$

$k_{TMAG} = 2.57 \pm 0.09 \times 10^{-6}$, sec.$^{-1}$

$k_{fL} = 1.63 \pm 0.20 \times 10^{-6}$, sec.$^{-1}$

TABLE XL

DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (0.01M) IN 1.14893N SODIUM HYDROXIDE; 1.0F SODIUM p-TOLUENESULFONATE AT 170.4 ± 0.2°C.

Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.00	9.086	20.70	8.134
1.25	8.867	28.45	8.027
2.50	8.953	29.40	7.888
8.20	8.632	36.70	7.537
12.40	8.384	48.15	7.444
13.50	8.614	49.10	7.256

$k_{dL} = 71 \pm 4 \times 10^{-6}$, sec.$^{-1}$

TABLE XLI

DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (0.01M) IN 0.9969N SODIUM HYDROXIDE; 1.5F SODIUM p-TOLUENESULFONATE AT 170.0 ± 0.1°C.

Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.80	8.816	24.75	8.046
1.95	8.944	33.80	7.850
7.40	8.480	34.90	7.832
8.60	8.556	46.30	7.492
14.80	8.242	47.55	7.486
15.80	8.170	60.25	7.223
23.70	8.063	61.40	7.457

$k_{dL} = 52 \pm 4 \times 10^{-6}$, sec.$^{-1}$

TABLE XLII

DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (0.01M) IN 0.4955N SODIUM HYDROXIDE; 2.0F SODIUM p-TOLUENESULFONATE AT 169.4 ± 0.1°C.

Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.00	9.258	28.60	8.763
1.20	9.085	39.90	8.736
9.90	9.040	40.90	8.600
10.90	9.036	57.30	8.458
18.80	8.914	71.25	8.261
19.95	8.848	72.40	8.409

$\underline{k}_{\underline{dL}} = 22 \pm 2 \times 10^{-6}$ sec.$^{-1}$

TABLE XLIII

DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (0.01M) IN 0.9979N SODIUM HYDROXIDE AT 169.9 ± 0.1°C.

Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$
0.00	9.643	24.70	8.740
0.85	9.652	32.10	8.586
6.55	9.265	33.15	8.448
7.65	9.181	42.40	8.047
15.90	9.045	43.35	8.116
17.05	8.996	53.25	7.899
23.75	8.680	54.05	7.840

$\underline{k}_{\underline{dL}} = 62 \pm 3 \times 10^{-6}$ sec.$^{-1}$

TABLE XLIV

DEGRADATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (0.01M) IN 0.5010N SODIUM HYDROXIDE AT 169.8 ± 0.4°C.

Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$	Time, min.	1,6-Anhydroglucose $\frac{\text{mole}}{\text{liter}} \times 10^3$
2.60	8.746	35.10	8.220
3.50	8.211	45.70	7.950
12.00	8.541	46.60	7.978
12.85	8.655	63.20	7.664
19.90	8.453	80.20	7.398
20.80	8.469	81.30	7.329

$k_{dL} = 34 \pm 4 \times 10^{-6}$, sec.$^{-1}$